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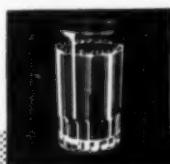
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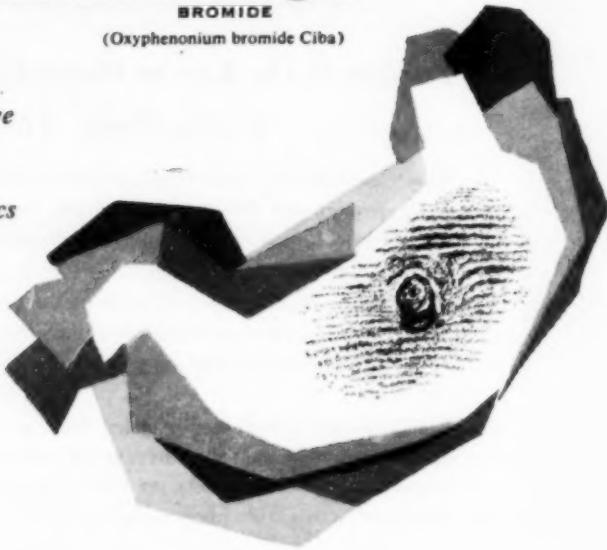
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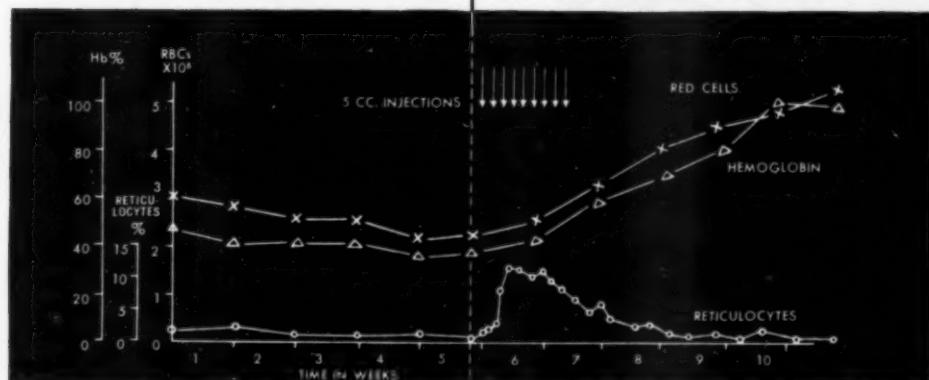
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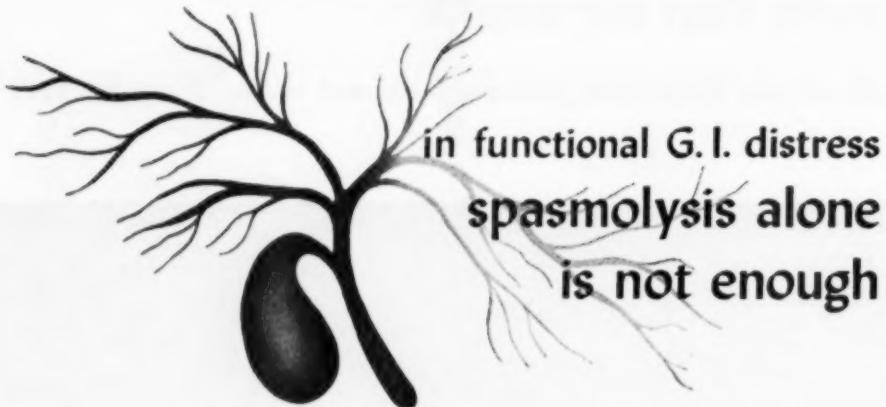
1. Dickstein, B., et al.: Am. J. Dis. Child. 84:52 (July) 1952.

FEOJECTIN*

a saccharated iron oxide
for safe intravenous injection

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.



For prompt and more effective relief of belching,
bloating, flatulence, nausea, indigestion and constipation,
prescribe *Decholin/Belladonna* for

reliable spasmolysis

- inhibits smooth-muscle spasm
- suppresses incoordinate peristalsis
- facilitates biliary and pancreatic drainage



improved liver function

- increases bile flow and fluidity through *hydrocholeresis*
- enhances blood supply to liver
- provides mild, natural laxation — without catharsis

DECHOLIN® with BELLADONNA

Dosage: One or, if necessary, two
Decholin/Belladonna Tablets three times daily.

Composition: Each tablet of *Decholin/Belladonna*
contains *Decholin* (dehydrocholic acid, AMES) 3½ gr.,
and ext. of belladonna, 1/6 gr. (equivalent to
tincture of belladonna, 7 minimis). Bottles of 100.

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8 hours' relief from a single dose

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TABLETS

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less frequent dosage
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greater freedom from side effects

PRANTAL*

3 forms
for more
flexible therapy

PRANTAL Repeat Action Tablets, 100 mg.
Dosage: One or two tablets every eight hours.

PRANTAL Tablets (plain), 100 mg., scored.
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PRANTAL Injection (subcutaneous or
intramuscular), 25 mg. per cc., 10 cc. vials.
Dosage: 0.5 mg. per Kg. of body weight
every six hours.

*T.M. Brand of diphenmethanil methylsulfate

Schering CORPORATION • BLOOMFIELD, NEW JERSEY

PRANTAL RA



THE PRACTICABLE SOLUTION OF

A patient on Obedrin Tablets can maintain a restricted diet, in comfort and lose excess weight fairly rapidly, without undesirable side effects.

Each Obedrin Tablet contains:

SEMOXYDRINE HYDROCHLORIDE, 5 mg.

(Methamphetamine Hydrochloride)

Suppresses appetite, elevates mood.

THIAMINE HYDROCHLORIDE, 0.5 mg.;

RIBOFLAVIN, 1 mg.; NIACIN, 5 mg.

Dose of these essential vitamins is adequate to supplement the 60-10-70 Diet, yet low enough to prevent stimulation of appetite.

ASCORBIC ACID, 100 mg.

A large dose, to help mobilize tissue fluids, so often a problem in obese patients.

PENTOBARBITAL, 20 mg.

To avoid excitation and insomnia; counteracts undesirable cerebral stimulation of methamphetamine. Does not diminish the anorexigenic action of methamphetamine.

A complimentary pad of 60-10-70 Basic Diet Sheets and a trial supply of Obedrin sent to physicians on request.

obesity
control



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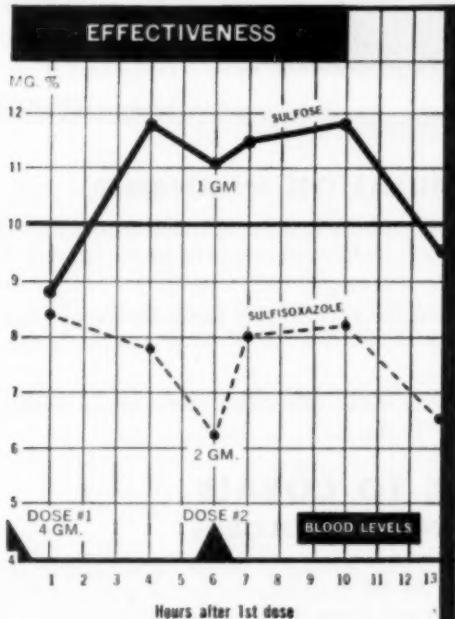
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S.E. Massengill

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WYETH

SUPPLIED: Bottles of 1 pint. Each teaspoonful (5 cc.) supplies 0.5 Gm. total sulfonamides (0.167 Gm. each of Sulfadiazine, Sulfamerazine and Sulfamethazine) in a special alumina gel suspension

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0.5 Gm.; bottles of 100



PIONEERING THE FIRST TRUE HEMATOPOIETIC STIMULANT

SPECIFIC BONE MARROW STIMULATION IN ANEMIA

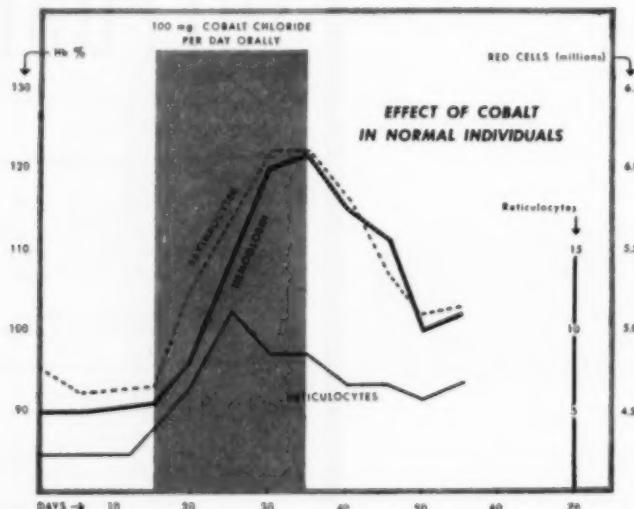
Medical research has recently proved that full therapeutic doses of cobalt exert a consistent and pronounced hematopoietic effect on bone marrow—a property which has not been demonstrated by any other compound.

Roncovite, the pioneer cobalt-iron preparation, has a remarkably rapid stimulating effect on the human blood producing mechanism. Because of this action, Roncovite opens an entirely new field in the therapy of human anemia.

The mechanism of the "cobalt effect" has been shown to differ completely from the "catalytic" effect of trace elements and from that of vitamin B₁₂.

HEMATOPOIETIC RESPONSE TO COBALT EFFECT ON ERYTHROGENESIS AND HEMOGLOBIN

Pharmacologically and clinically, it is now well established that cobalt administration causes a rapid and striking hematopoietic response. An initial increase in reticulocytes is promptly followed by pronounced increases in the red cell count and in hemoglobin.⁽¹⁻²⁷⁾ The bone marrow undergoes progressive hyperplasia of all cellular elements⁽¹³⁾ and shows increased numbers of erythrocyte precursors.^(1,9)



In experimentally induced anemia, cobalt accelerates recovery from hemorrhage,⁽¹⁾ overcomes the hemopoietic depression due to inflammation⁽¹⁰⁾ and is superior to iron, copper-iron, liver extract or vitamin B₁₂ in preventing the anemia produced by hypophysectomy.⁽²⁴⁾

In iron resistant secondary anemia of infants and children an average weekly gain of 250,000 erythrocytes and 0.6 to 0.7 Gm. of hemoglobin has been reported.^(13,27)

RONCOVITE

RONCOVITE (COBALT AND IRON) FOR FULL EFFECT

The erythropoietic effect of cobalt does not depend on the presence of iron, since cobalt administration alone will cause erythropoiesis even in the presence of iron deficiency and may lead, in this way, to a hypochromia.⁽¹⁹⁾ Since iron is necessary for hemoglobin synthesis, Roncovite provides ferrous sulfate to insure adequate iron reserves and thus permits hemoglobin increases to accompany erythropoiesis under the influence of cobalt.

CLINICAL APPLICATIONS OF RONCOVITE

Cobalt therapy has given excellent results in secondary anemia accompanying chronic inflammatory diseases, infections, tuberculosis, chronic hemorrhage, pregnancy, iron deficiency anemia, idiopathic hypochromic anemia, erythropoietic hypoplastic and hypochromic microcytic anemia.

PREPARATIONS AVAILABLE

RONCOVITE TABLETS

each enteric coated, red tablet contains:

Cobalt chloride.....	15 mg.
(Cobalt as Co..... 3.7 mg.)	
Ferrous sulfate, exsiccated.....	0.2 Gm.
(Iron as Fe..... 60 mg.)	

Average adult dosage—1 tablet after each meal and at bedtime.

Supplied in bottles of 100 tablets.

RONCOVITE DROPS

each 0.6 cc. contains:

Cobalt chloride.....	40 mg.
(Cobalt..... 9.9 mg.)	
Ferrous sulfate.....	75 mg.
(Iron..... 15.1 mg.)	

Average dose—0.6 cc. (10 minims) diluted with water, milk, fruit or vegetable juice once daily to infants and children.

Supplied in bottles of 15 cc. with calibrated dropper.

Complete bibliography on request.

LLOYD BROTHERS, Inc., Cincinnati 3, Ohio

IN THE INTEREST OF MEDICINE SINCE 1870

3

Useful Cardiac Drugs

① Thesodate — Brewer IN ANGINA PECTORIS

(Theobromine Sodium Acetate $7\frac{1}{2}$ gr. enteric coated)

Thesodate has been proven effective in increasing the capacity for work in individuals suffering from coronary artery disease. One Thesodate tablet four times a day (after meals and at bedtime) helps to maintain improved heart action and increased coronary artery circulation.

② Enkide — Brewer IN LUETIC HEART DISEASE

(Potassium Iodide one gram or half gram enteric coated)

Enkide is useful as an adjuvant in tertiary syphilis and wherever potassium iodide therapy is indicated. Enkide insures accuracy of dosage, absence of gastric irritation and convenience of administration. Patients are more apt to follow prescription directions because of these advantages.

③ Amchlor — Brewer IN CARDIAC EDEMA

(Ammonium Chloride one gram enteric coated)

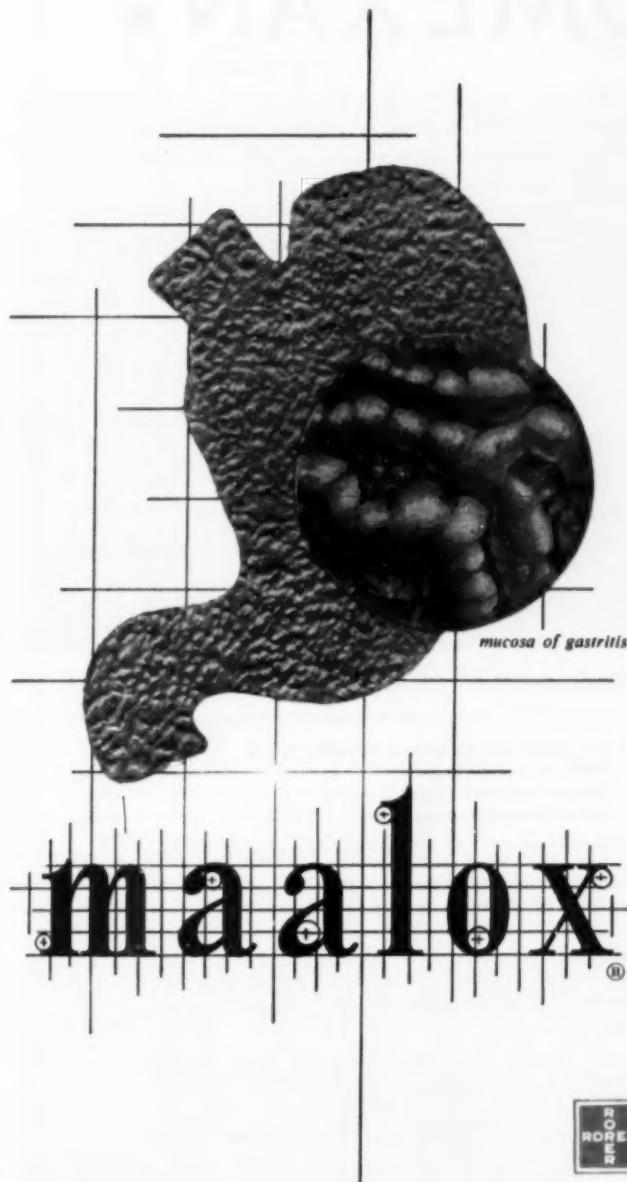
Amchlor cuts in half the number of tablets each patient takes when large amounts of ammonium chloride are prescribed. This convenience to the patient helps to insure full and complete use of the entire amount prescribed. Amchlor is useful in cardiac edema, hypertension, dysmenorrhea, Meniere's Syndrome, etc.

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Suspension Maalox-Rorer
is a colloidal suspension
of the hydroxides of
Magnesium and Aluminum.
It is pleasant to taste.
Continuous clinical use
has demonstrated that
it causes a *quick satisfactory*
relief of pain and
discomfort caused by
gastritis.

The dose is two to four
fluidrachms.

supplied: In 355 cc.
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Also in tablets (Each Maalox
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fluidrachm of Suspension).
*Samples will be sent promptly
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"Tromexan is a safer drug . . . its shorter action and larger daily dose allow more ready regulation of the anticoagulant therapy. The risks of prolonged over-dosage with the associated hemorrhagic tendencies are correspondingly reduced." Tollef, J. A., and Gilchrist, A. R.: Am. Heart J. 47:864, 1954.

"Tromexan appears to produce few hemorrhagic manifestations . . ."

Wright, Irving S.: Med. Med. 19:55, 1951.

Indications

- *Thrombophlebitis*
- *Coronary Thrombosis*
- *Pulmonary Embolism*
- *Auricular Fibrillation with Embolization*
- *Congestive Heart Failure (selected cases)*
- *Postoperative and Postpartum Prophylaxis (selected cases)*

A SIMPLE SCHEDULE OF TROMEXAN DOSAGE IS AS FOLLOWS:

<i>First 24 hours</i>	Initial Loading Dose — 1500 mg.
<i>Second 24 hours</i> (Suggested 24-hour maintenance dose in divided amounts)	If prothrombin-time 24 hours after loading dose is: Above therapeutic range* 300 mg.† Within therapeutic range 600 mg. Below therapeutic range 900 mg.
<i>Third 24 hours</i> and each succeeding 24-hour period	Adjust maintenance dosage (average 600-900 mg. daily) to produce a prothrombin-time two to two and one-half times normal

*Therapeutic range is interpreted as 2-3½ times the normal prothrombin-time in seconds.

†This dose should not be administered until a second prothrombin determination has indicated the prothrombin-time has returned within therapeutic range.

Despite its qualities which allow for greater safety, TROMEXAN therapy should always be controlled by periodic prothrombin-time determinations. A detailed brochure fully describing the method of use of TROMEXAN will gladly be sent on request.

TROMEXAN (brand of ethyl bisoumacetate): Available in tablets of 150 mg. and 300 mg.

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220 Church St., New York 13, N. Y.

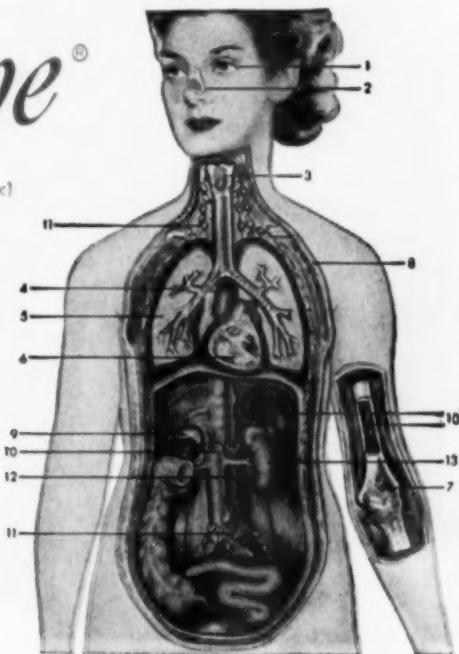


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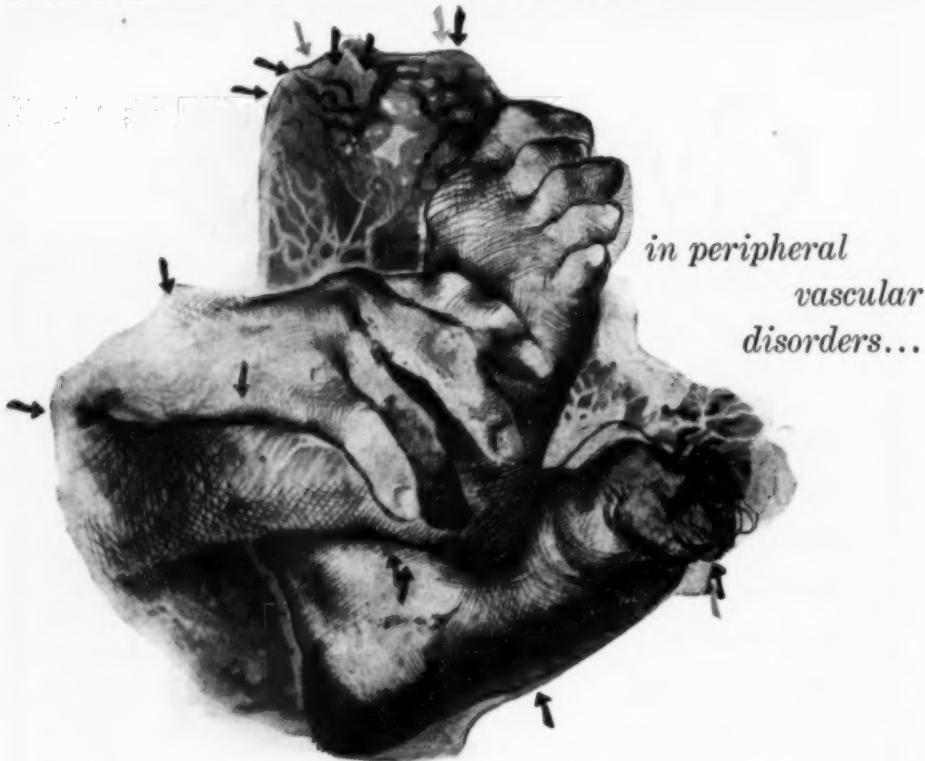
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*orally and
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peripheral vasodilator*

Virtually as effective by oral as by intravenous or intramuscular administration, this unusually potent vasodilator may be expected to induce cumulative benefits in both functional and obstructive peripheral vascular disorders.

Supplied as Tablets of 25 mg., in bottles of 100 and 1000. Elixir, 25 mg. per 4 cc., bottles of 1 pint. Multiple-dose vials, 10 cc., containing 25 mg. per cc. Ciba Pharmaceutical Products, Inc., Summit, New Jersey

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Abbott

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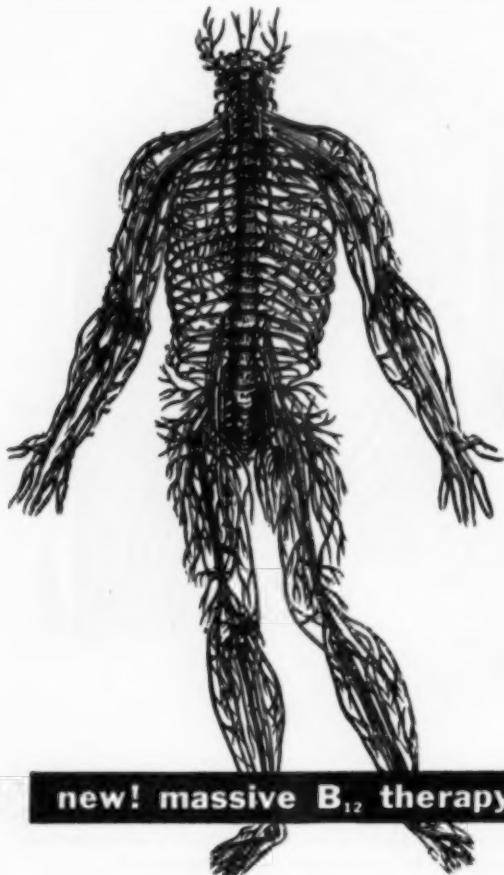
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Thiamine Mononitrate, 6 mg.
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(2XRDA†)
Pyridoxine
Hydrochloride..... 1 mg.
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Pantothenic Acid..... 10 mg.
Liver Fraction 2,
N.F..... 0.3 Gm. (5 grs.)
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SUR-BEX WITH VITAMIN C
contains 150 mg. of ascorbic
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**DODECAVITE CRYSTALLINE
1000 mcg. vitamin B₁₂ per cc.
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Complete or long-time remission of pain in a substantial number of patients • often successful where all other therapy has failed • non-toxic • well worth trying in these disabling, agonizing pain conditions which so often leave the physician so helpless and the patient so hopeless.

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In the form of AMINODROX, three out of four patients can be given therapeutically effective *oral* doses of aminophylline.

This is possible with AMINODROX because gastric disturbance is avoided.

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Also available with 1 gr. phenobarbital.

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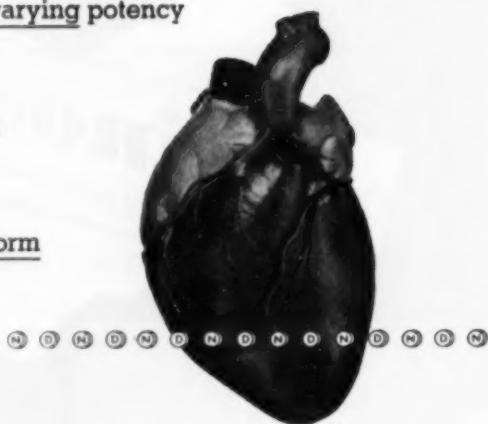
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Ovaltine is available in two varieties, plain and chocolate flavored, giving choice according to preference. Serving for serving, both varieties are virtually alike in their wealth of nutrients.

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Three Servings of Ovaltine in Milk Recommended for Daily Use Provide the Following Amounts of Nutrients

(Each serving made of $\frac{1}{2}$ oz. of Ovaltine and 8 fl. oz. of whole milk)

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CHLORINE	900 mg.
COBALT	0.006 mg.
COPPER	0.7 mg.
FLUORINE	3.0 mg.
*IODINE	0.15 mg.
*IRON	12 mg.
MAGNESIUM	1.20 mg.
MANGANESE	0.4 mg.
*PHOSPHORUS	940 mg.
POTASSIUM	1300 mg.
SODIUM	560 mg.
ZINC	2.6 mg.

VITAMINS

*ASCORBIC ACID	37 mg.
BIOGIN	0.03 mg.
CHOLINE	200 mg.
FOLIC ACID	0.05 mg.
*NIACIN	6.7 mg.
PANTOTHENIC ACID	3.0 mg.
PYRIDOXINE	0.5 mg.
*RIBOFLAVIN	2.0 mg.
*THIAMINE	1.2 mg.
*VITAMIN A	3200 I.U.
VITAMIN B ₁₂	0.005 mg.
*VITAMIN D	420 I.U.

*PROTEIN (biologically complete)

32 Gm.

*CARBOHYDRATE

65 Gm.

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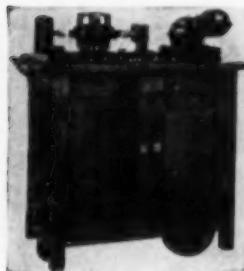
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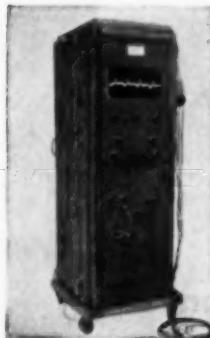
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Cardalin

with safety and simplicity
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offer distinct advantages over any
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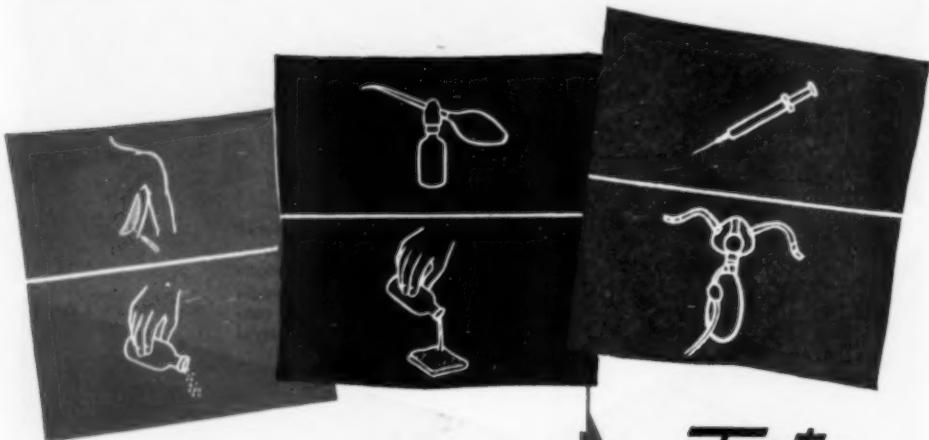
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Cardalin contains 5 grains of aminophylline per tablet... the highest concentration supplied for oral administration. Two protective factors (Aluminum Hydroxide and Ethyl Aminobenzoate) counteract the local gastric irritation so common to oral aminophylline therapy. Extensive clinical studies have established the excellent therapeutic action of Cardalin.

Cardalin—Each Cardalin tablet contains: Aminophylline, 5 grains; Aluminum Hydroxide, 2.5 grains; Ethyl Aminobenzoate, 0.5 grains. Cardalin is best tolerated after meals and preferably administered with one-half glassful of milk.

Cardalphen now available containing phenobarbital (1/4 gr. per tablet).



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- powder blower
- dusting
- intrapleural infusion
- injection
- aerosol

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The Armour Laboratories Brand of Highly Purified Crystalline Trypsin

ACTION AND BENEFITS OF THIS NEW ENZYME

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Tryptar Aerosol

FOR USE BY INHALATION

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- Bronchiectasis
- Purulent Bronchitis (acute and chronic)
- Emphysema
- Atelectasis
- Pneumonitis

Supplied: Tryptar Aerosol is supplied in a package containing: 125,000 Armour Units (125 mg. of trypic activity) of highly purified crystalline trypsin per vial, plus an ampule containing 3 cc. of Tryptar Diluent.



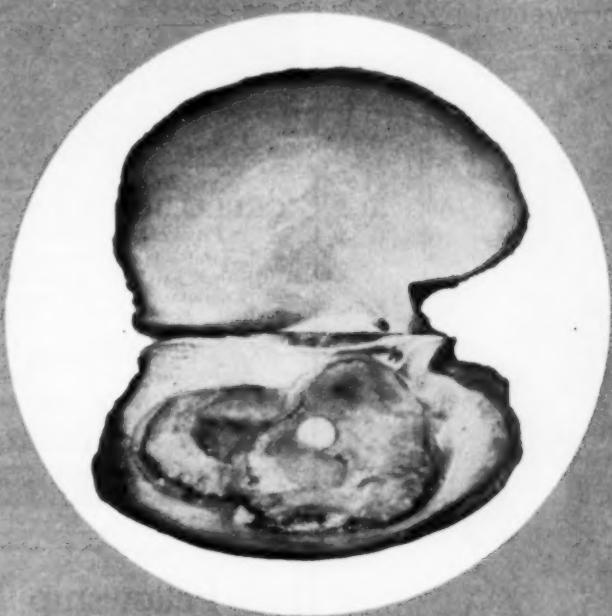
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1. Gewin, H. M., and Friis, G. J.: *Yale Jour. Biol. & Med.*, 23:332, Feb., 1951.

2. Marshall, H. C., Jr., Palmer, W. L., and Kirsner, J. S.: *J. A. M. A.*, 144:900, Nov. 11, 1950.

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1. Humphreys, P., et al.: *Angiology* 3:1 (Feb.) 1952.
2. Plotz, M.: *N.Y. State J. Med.* 52:2012 (Aug. 15) 1952.

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1. Cantor, A. J., Am. J. Proctol. 3:204-210, (Sept.) 1952.

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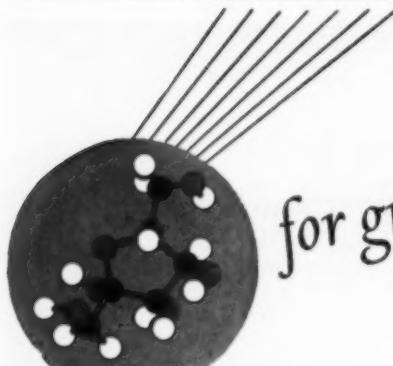
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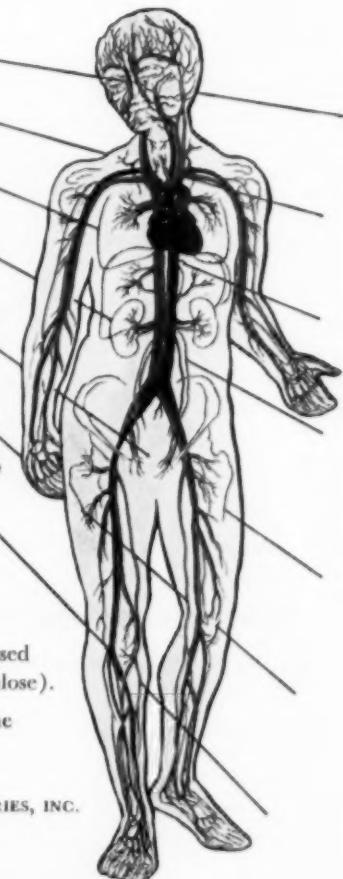
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1. Bigger, J.W.: Lancet, 2:46, 1950.

2. Herrell, W.E.: *Penicillin and Other Antibiotic Agents*, W.B. Saunders, Philadelphia, 1945.

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ENDOCRINE REGULATION OF THE BLOOD SUGAR *

By JEROME W. CONN, M.D., F.A.C.P., *Ann Arbor, Michigan*

OF all of the presently recognized metabolic disturbances which arise in man as the result of deranged endocrine function, diabetes mellitus is the most common. As a clinical entity it has been known, studied and treated by physicians for many years. Because of the tremendous impact upon medical science of the isolation of insulin by Banting and Best in 1921, the historical details of the disease itself are known to virtually all whose interests fall into the general realm of biology. Much of our present knowledge in the fields of nutrition, metabolism and modern endocrinology stems from basic facts derived from careful study of diabetic patients and of experimentally produced diabetes in animals. Because of periodic advances it is proper that we, as clinicians, reexamine from time to time the sum total of knowledge available to us from both the clinical and the animal laboratories. I shall discuss the various physiologic functions which normally affect the metabolism of carbohydrate and which, when properly integrated, result in what we call a normal level of circulating blood sugar.

At the outset, several points regarding the over-all control of carbohydrate metabolism should be made clear. First, the organs and tissues involved in the regulation of carbohydrate metabolism and hence the blood sugar are reasonably well known. This knowledge is based upon experiments involving organ removal or administration of organ extract. Thus, removal of one organ results in a rise of the blood sugar; whereas removal of another results in a fall. Injection of materials extracted from these organs produces the reverse effect. While the final effects are known, our knowledge of the intracellular enzymatic changes which occur under these circumstances is relatively meager. The current investigator of metabolic processes finds himself struggling at the cellular level with problems much more complex than those heretofore encountered. No doubt the enzyme chemist will eventually broaden our knowledge of how hormones regulate

* From the Symposium on Diabetes, presented at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 25, 1952.

the rates at which fundamental biochemical reactions proceed within the cell. In the light of present information, however, the clinician is less interested in the intermediary metabolic effects than in the end result of a given disturbance. If his patient exhibits either hyperglycemia or hypoglycemia he wants to know where to look for the primary cause of the difficulty.

The second point worthy of mention is that experimental removal of an organ, or injection of a hormone, concerned in the regulation of carbohydrate metabolism, so upsets the integrated system of checks and balances that secondary, often compensatory functional changes occur in other elements of the system. This makes it extremely hazardous to assign specifically to the organ removed, or to the hormone injected, all of the changes observed.

Third, the initiating cause of the garden variety of diabetes mellitus in man remains unknown, involving as it does the imponderable hereditary element. In clinical medicine we do recognize certain unusual types of diabetes as being analogous to those experimentally produced in animals, as, for example, in acromegaly, in Cushing's syndrome, in pheochromocytomas, following total pancreatectomy, etc., but whether initiating factors such as these play a rôle in the etiology of the usual type of diabetes mellitus remains to be proved. However, once the ordinary variety of diabetes has been permanently established, whatever may be the inciting factors, it is clearly a situation then characterized by the absence of sufficient insulin activity. I emphasize the term "insulin activity" because lack of insulin activity may well be due to too little production of insulin, but it is possible to have normal or even supernormal production of insulin and still have depressed insulin activity, either because insulin is being destroyed or because its activity is being depressed by antagonistic substances.

With these thoughts in the background, we may proceed with our discussion of the hormonal regulation of the blood sugar.

Carbohydrate metabolism is controlled by a complex integration of organs, tissues and glands of internal secretion. Importantly involved are the central nervous system, the autonomic nervous system, the gastrointestinal tract, the liver, the kidneys, the peripheral tissues (mainly the muscles), the pancreas, the adrenal cortex and medulla, the anterior pituitary gland and, to a lesser extent, the thyroid. Inasmuch as hormones are merely rate-regulators of fundamentally independent metabolic processes which occur in the organs and tissues of the body, it is convenient in discussing the problem to separate it into two parts, namely, the metabolic phase and the hormonal influence.

THE METABOLIC PHASE

At all times the level of sugar in the blood is the resultant of the rate at which it enters the blood stream and the rate at which it leaves the blood. What, then, are the sources of blood sugar? In the absorptive state it is predominantly the carbohydrate of the diet. Its rate of entry into the blood

stream is governed by the rate of intestinal absorption. In the fasting state the liver is usually regarded as the sole direct source of glucose to the blood, although recent work¹ indicates that under certain conditions the kidney may actually add glucose to the blood. During fasting the liver gradually gives up its store of preformed glycogen and, in addition, makes glycogen from noncarbohydrate precursors, mainly through the process of glycogenesis from protein. Lactic acid derived from muscle glycogen is also converted in the liver to glycogen. Hepatic glycogen derived from these sources is gradually released as glucose to the blood. These, then, are the only sources of glucose to the blood.

What fundamental processes remove glucose from the blood? In the presence of a plethora of glucose from absorption a large percentage of it is rapidly converted to fat. Some is oxidized to carbon dioxide and water in the cells, and some is deposited, as glycogen for the most part, in the liver and the muscles. In the fasting state, peripheral oxidation of glucose becomes the major consumer of blood glucose, since deposition of fat and glycogen from blood glucose is not occurring. However, peripheral oxidation of glucose under these circumstances becomes sharply curtailed, and the blood glucose level is then maintained by relatively small additions of glucose from the liver.

THE ENDOCRINE INFLUENCE

The hormonal influences are upon enzymatic reactions, and they control the rates at which the various processes already delineated proceed. Where apparent antagonism exists between one hormone and another, it is at the cellular level rather than as the result of a direct effect of one hormone upon another one.

The Islets of Langerhans: The islets of Langerhans produce one proved hormone, insulin, which is derived from the beta cells. Another factor not yet proved to be a hormone and thought to be produced by the alpha cells has been designated as the hyperglycemic-glycogenolytic factor.

What does insulin do? Of all of the known hormonal influences upon carbohydrate metabolism, only one hormone is capable of reducing the blood sugar level of the fed animal, and that hormone is insulin. All of the other known hormones either raise the blood sugar or do not influence it. Insulin lowers blood sugar by virtue of the following activities:

1. It promotes formation of fatty acid from glucose.
2. It promotes peripheral oxidation of glucose. It is believed² that the first step in this process involves the ability of insulin to release the enzyme, hexokinase, from the state of inhibition in which it is held by an anterior pituitary hormone.
3. It increases the rate of formation of liver and muscle glycogen.
4. Under some circumstances it decreases glycogenesis from protein.
5. It appears to be a necessary participant in the synthesis of tissue protein from amino acids.

Thus it can be stated that all of the known primary metabolic defects which are recognized in the diabetic patient are reversible by the action of insulin.

The so-called alpha cell hormone³ of the islets may yet prove to be an artifact rather than a normally produced physiologic substance, but at present one must keep an open mind. The effect of this material when given intravenously to man or to animals is to raise the blood sugar. So far as is known, this is accomplished solely by its glycogenolytic action on the liver. This material is contained in all of the insulin preparations commercially available in this country. Its removal as a contaminant would probably conserve significant amounts of insulin, since that fraction of insulin utilized in overcoming the hyperglycemic effect of the contaminant would be saved. The recent work of Young and his colleagues⁴ suggests that growth hormone

INTACT ANIMAL	DOG	CAT	DIABETES	FASTING HYPOGLYCEMIA	'HOSSAY ANIMAL'	DIABETES	PERMANENT DIABETES	PERMANENT DIABETES
ANT. PIT.	○		○	○	○	○	○	○
PANCREAS	○		○	○	○	○	○	○
ADRENAL CORTICES	○	○	○	○	○	○	○	○
FASTING HYPOGLYCEMIA	○		○	○	○	○	○	○
'LONG ANIMAL'	○		○	○	○	○	○	○
NO DIABETES	○		○	○	○	○	○	○
DIABETES	○		○	○	○	○	○	○
DIABETES	○		○	○	○	○	○	○
DIABETES	○		○	○	○	○	○	○
TRANSIENT DIABETES	○		○	○	○	○	○	○
			APE →		APE →		APE →	
				ACE →		ACE →		ACE →
								COMPOUNDS FOR E →

FIG. 1.

not only stimulates increased production of pancreatic insulin but may also increase the output of the hyperglycemic-glycogenolytic factor of the alpha cells.

We now turn from the pancreas to those endocrine glands which, by their influence, tend to raise the level of the blood sugar. These are the anterior pituitary, the adrenal cortex, the adrenal medulla and the thyroid. The latter two appear to be much less influential directly than the anterior pituitary gland and the adrenal cortex. For background, let us review briefly the classical established gross physiologic relationships between the pancreas, the anterior pituitary gland and the adrenal cortex.

Figure 1 is intended to illustrate primary facts in these relationships derived from animal experimentation. An x over an organ indicates that it has been removed surgically. An arrow indicates injection into the animal of a designated material. Proceeding from left to right in the upper columns

one notes first the von Mering and Minkowski experiment of total pancreatectomy and a resultant diabetes. Hypophysectomy, on the other hand, produces severe and often fatal hypoglycemia, if such a preparation receives no food for a very short period of time. The classic Houssay experiment of removing both the pancreas and the pituitary gland produced a preparation which exhibited a greatly ameliorated form of diabetes. The blood sugar of such an animal fluctuates widely and in an uncontrolled way. Fasting produces hypoglycemia, while hyperglycemia occurs upon the ingestion of food. The next column indicates that administration of crude anterior pituitary extract to the Houssay preparation results in a prompt return of severe diabetes. Thus it became clear that for pancreatic diabetes to manifest itself in the usual ways certain secretions of the anterior lobe of the pituitary gland were necessary. It was then demonstrated by the Houssay school that injections of crude anterior pituitary extract into normal dogs produced a transient hyperglycemia. This work was followed up by that of Young,⁵ who found that persistent administration of crude anterior pituitary extracts to normal dogs resulted in diabetes mellitus which persisted for as long as two years after injections of the extract had been discontinued. It was demonstrated, further, that in such animals marked degeneration of the beta cells of the islets of Langerhans had occurred, and that the persistent diabetes was really due to insulin deficiency.⁶ This was the first demonstration that a normal animal could be given pancreatic diabetes by the administration of excessive amounts of hormonal material from an extra pancreatic organ. This type of diabetes has been called metahypophyseal diabetes. More recently, this same type of diabetes has been produced in normal animals by the injection of small amounts of pure growth hormone.⁷

The lower columns in figure 1 bring into the picture the rôle played by the adrenal cortices. For many years it has been known that fasting hypoglycemia is characteristic of patients with Addison's disease. The same is true of the adrenalectomized animal, fasted for a short period of time. Because a similar type of fasting hypoglycemia occurs in either the adrenalectomized animal or the hypophysectomized animal, Long and Lukens thought that perhaps Houssay's amelioration of pancreatic diabetes by hypophysectomy might have occurred by virtue of the loss of pituitary ACTH and the accompanying loss of adrenal cortical function. With this idea in mind, they removed both adrenal glands of depancreatized cats. A prompt amelioration of the diabetes occurred, and the carbohydrate metabolism of this preparation was found to be similar indeed to that observed in the Houssay animal. It was further found that the administration of crude anterior pituitary extract to the "Long animal" produced no exacerbation of the diabetes, while administration of adrenal cortical extract produced a prompt recrudescence of the diabetic state. These experiments seemed to be in accord with the hypothesis of Long and Lukens until it was realized that crude anterior pituitary extract is capable of exacerbating the diabetes of the "Long animal," provided a very small amount of adrenal cortical

extract is supplied simultaneously. This amount of adrenal cortical extract cannot of itself produce a recrudescence of the diabetic state in the depancreatized-adrenalectomized animal. It then became clear that something other than ACTH, which is contained in crude anterior pituitary extract, was greatly diabetogenic, but that for it to exert its full diabetogenic effect a small amount of adrenal cortical hormone had to be present. It gradually became evident that the potent diabetogenic material in the crude pituitary extract was probably growth hormone, but that a minimal level of adrenal cortical function was necessary for the growth hormone to exert its full diabetogenic action. On the other hand, it is also true that *large* amounts of adrenal cortical extract produce a return of severe diabetes in the Houssay preparation. Similarly, large amounts of Compound F or Compound E are capable of producing diabetes in the intact animal. To date, however, permanent diabetes in animals has not been produced by the administration of cortical hormones.

The Anterior Pituitary Gland: From the various relationships described above it seems clear that two anterior pituitary hormones, growth hormone and adrenocorticotropin, are involved in bringing about the metabolic consequences of total pancreatectomy. It is an interesting fact, however, that pure growth hormone is intensely diabetogenic when administered to intact dogs or cats but that this has not been found to be the case in the rat or in man. ACTH, on the other hand, produces hyperglycemia in the latter two species, while the dog and the cat are very resistant to its diabetogenic effect. Nevertheless, the two pituitary hormones known to be capable of inducing hyperglycemia are the growth hormone and ACTH. By what means is hyperglycemia produced by each of these substances?

Growth Hormone: Inasmuch as administration of growth hormone to the Houssay preparation causes prompt exacerbation of the diabetes, it is obvious that under these conditions, at least, the marked diabetogenicity of growth hormone is extra-pancreatic in nature. There is, indeed, much evidence to indicate that under the influence of excessive amounts of growth hormone an inhibition of peripheral oxidation of glucose occurs. There is much to suggest that this action of growth hormone comprises its major potentiality in raising blood sugar.

When the pancreas of the animal is *in situ*, however, clear-cut pancreatic effects of administration of growth hormone appear. Growth hormone administered to puppies gives evidence of increased insulin production and no hyperglycemia. When given to adult cats and dogs there appears to be an initial increase in islet cell activity, followed quickly by hyperglycemia and islet cell degeneration. It is believed by some that growth hormone has a direct effect upon pancreatic islet cells, stimulating them to increased insulin secretion, that excessive stimulation of the islets in this way leads to degeneration from overwork and permanent diabetes, and that in the young growing animal the islets appear capable of responding to increased

stimulation without degeneration. That growth hormone may have a direct insulotrophic effect upon the islets is still possible. The alternative explanation of the above mentioned phenomena is based upon the known effect of growth hormone in blocking peripheral utilization of glucose. According to this concept, growth hormone increases the peripheral need for insulin. The increased secretory activity and ultimate islet cell degeneration seen in the pancreas are than considered to be a secondary phenomenon.

The known effects of growth hormone upon the synthesis of protein and upon general growth, taken in conjunction with its different effects upon carbohydrate metabolism when applied to the young versus the adult animal, are interesting points about which to speculate. Actual knowledge in this area, however, is very incomplete. Engle et al.⁶ have shown that, while growth hormone fails to produce diabetes in the rat, the combined administration of growth hormone and ACTH results consistently in glycosuria and hyperglycemia. Since the protein anabolic effect of growth hormone can be overcome by the protein catabolic effect of ACTH, they suggest that interference with the growth promoting activity of growth hormone allows it, in a presently unexplained way, to exert its full diabetogenic potentiality.

ACTH and the Adrenal Cortex: ACTH and the adrenal cortical hormones must be considered together, since the effects of ACTH upon carbohydrate metabolism are solely due to the capacity of this hormone to stimulate increased secretion of adrenal cortical hormones. It is now established that the adrenal cortical hormones which affect carbohydrate metabolism are those of the 11-oxygenated type, such as cortisone and hydrocortisone (Compound F). These steroids raise blood sugar through two major activities.^{8, 10, 11} First, they increase the rate of glycogenesis from protein. Second, they too depress the rate of tissue utilization of carbohydrate. These activities of adrenal cortical hormone are responsible for the prevention of the fasting hypoglycemia which occurs in adrenal cortical insufficiency of man or animals. It should be restated at this point that these hormones are capable of inhibiting growth because of their capacity to increase the breakdown of body protein.

Thus we are presented with an extremely interesting metabolic phenomenon which to date remains unexplained. Two anterior pituitary hormones, growth and ACTH, tend to raise the blood sugar. Each, per se, depresses tissue utilization of glucose and can exacerbate the diabetes of the hypophysectomized-depancreatized preparation. ACTH, however, results in protein catabolism and glycogenesis from protein, while growth hormone is protein anabolic. When the protein anabolic effect of growth hormone can be accomplished this hormone fails to be diabetogenic. This must in some way be related to the presence of insulin activity. When growth hormone is prevented from being protein anabolic (and this is probably related to the absence of sufficient insulin activity), it becomes diabetogenic.

The Adrenal Medulla: All are aware of the acute effect of epinephrine in raising blood sugar. This is accomplished by hepatic glycogenolysis. Lactic acid, which reaches the liver in increased quantities as the result of epinephrine activity, is an end product of the breakdown of muscle glycogen. In the liver it is resynthesized to glycogen. These pharmacologic effects of epinephrine are well recognized.

In addition, however, we are now aware that epinephrine causes a discharge of ACTH from the anterior pituitary gland.¹² Thus, to the established actions of epinephrine upon carbohydrate metabolism we must add the effects of adrenocortical hormone, which have already been discussed, namely, increased glycogenesis from protein and depressed peripheral oxidation of glucose.

Thyroid Hormone: Finally, and briefly, one may state that the effects upon carbohydrate metabolism of thyroid hormone are relatively minor. The major effect of this hormone is upon the rate of intestinal absorption of sugar.^{12, 14} Lack of the hormone results in slow absorption and excessive thyroid hormone produces rapid absorption. In the presence of excessive amounts of circulating thyroid hormone, certain indirect effects upon liver function may occur. Depleted stores of liver glycogen may occur as the result of excessive total energy requirements of the body. In chronic thyrotoxicosis, eventual hepatic damage may ensue which, *per se* may affect the normal control of the blood sugar level.

SUMMARY

An integrated system of humoral agents exists which controls, at the tissue level, the rates at which certain fundamental reactions proceed. Those reactions applicable to this discussion include conversion of glucose to fat, conversion of glucose to glycogen, oxidation of glucose to carbon dioxide and water, hepatic glycogenolysis, glycogenesis from protein, and synthesis of protein from amino acids. These cellular reactions are brought about by enzymes, which in turn are regulated by hormones. An aberration in the system leads to either hyperglycemia or hypoglycemia, since all of these fundamental reactions either add glucose to or subtract it from the blood.

Of all of the hormonal influences upon carbohydrate metabolism the most critical effects are exerted by the secretions of the pancreas, the anterior pituitary gland and the adrenal cortices. Epinephrine, although generally inducing a transitory effect, is capable of invoking the adrenal cortical influence by virtue of its capacity to bring about a discharge of ACTH from the pituitary gland.

The blood sugar level itself can exert an influence upon its own regulators. Hypoglycemia causes a discharge of epinephrine and sets off the eventual adrenal cortical response. Hyperglycemia, *per se*, is a stimulus to increased pancreatic insulogenesis.

Despite all of the newer knowledge, the factor or factors which initiate the diabetic state in man remain obscure. It is this inciting factor which is the elusive one. Once permanently established, diabetes mellitus in man appears to be a disease characterized by an insufficiency of insulin activity.

BIBLIOGRAPHY

1. Drury, D. R., Wick, A. N., and MacKay, E. M.: Formation of glucose by the kidney, *Am. J. Physiol.* **163**: 655, 1950.
2. Colowick, S. P., Cori, G. T., and Slein, M. W.: The effect of adrenal cortex and anterior pituitary extracts and insulin on the hexokinase reaction, *J. Biol. Chem.* **168**: 583, 1947.
3. Sutherland, E. W.: The effect of hyperglycemic factor of the pancreas and of epinephrine on glycogenolysis, *Recent Progress in Hormone Research* **5**: 441, 1950.
4. Bornstein, J., Reid, E., and Young, F. G.: The hyperglycaemic action of blood from animals treated with growth hormone, *Nature, London* **168**: 903, 1951.
5. Young, F. G.: Permanent experimental diabetes produced by pituitary (anterior lobe) injections, *Lancet* **2**: 372, 1937.
6. Richardson, K. C., and Young, F. G.: Histology of diabetes induced in dogs by injection of anterior-pituitary extracts, *Lancet* **1**: 1098, 1938.
7. Campbell, J., Lei, H. P., and Davidson, I. W. F.: Production of diabetes and increased erythrocyte sedimentation rate by purified growth hormone, *Endocrinology* **49**: 635, 1951.
8. Engle, F. L., Viau, A., Coggins, W., and Lynn, W. S.: Diabetogenic effect of growth hormone in the intact force-fed adrenocorticotrophin treated rat, *Endocrinology* **50**: 100, 1952.
9. Ingle, D. W.: The production of glycosuria in the normal rat by means of 17-hydroxy-11-dihydrocorticosterone, *Endocrinology* **29**: 649, 1942.
10. Ingle, D. W., Li, C. H., and Evans, H. M.: The effect of adrenocorticotrophic hormone on the urinary excretion of sodium chloride, potassium, nitrogen, and glucose in normal rats, *Endocrinology* **39**: 32, 1946.
11. Conn, J. W., Louis, L. H., and Johnston, M. W.: Studies upon mechanisms involved in the induction with adrenocorticotrophic hormone of temporary diabetes mellitus in man, *Proc. Am. Diabetes A.* **8**: 213, 1948.
12. Gershberg, H., Fry, E. G., Brobeck, J. R., and Long, C. N. H.: The rôle of epinephrine in the secretion of the adrenal cortex, *Yale J. Biol. and Med.* **23**: 32, 1950.

THE IMMUNOLOGIC ASPECTS OF ALLERGIC CONDITIONS *

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ONE of the prominent and important functions of the living cell, even in its most primitive forms, is its ability to cope with substances of foreign origin with which it has come into contact. Metchnikoff pointed out that unicellular organisms, such as the ameba, and many cells of complex structure, such as the metazoan bodies, employ this facility for nutritional purposes. Some cells of the higher forms of life may retain their ancestral trait of assimilating certain types of foods not ingested by first intention.¹ The majority of such cells, members of the reticuloendothelial system, aided by components of the body fluids, utilize as a mechanism of defense their specialized skill or aptitude of engulfing and ultimately disposing of foreign material which is embarrassing or dangerous to the body economy. In the majority of instances, such phagocytic action would appear to be simply a clearing mechanism, complete in itself, with no complications resulting. When, however, the invading material is highly provocative, as in the case of pathogenic organisms, profound alterations both persistent and specific usually develop, especially in the cytoplasm of the cell. A structural change occurs, the normal globulin becoming antibody globulin,² which has a special affinity for invading foreign material and a heightened capacity for its disposal.¹ The cells of the phagocytic system which hitherto have produced normal globulin have been potentiated to produce specific antibody, their original elementary scavenging capacity being supplemented by an ability to neutralize, upon subsequent exposure, foreign substance or antigen, by specifically combining with it. It is this specific alteration, this reaction of sensitized cell with antigen, that provides the basis for our present ideas of hypersensitivity in man and animal. This information has been obtained largely from immune studies upon the effect of pathogenic organisms upon man and upon the effect of nonpathogenic and pathogenic organisms, egg white and horse serum upon the lower animal. There are large gaps in our knowledge, but the fundamental concepts thus obtained from studies on the lower animal would seem to apply to the allergic man exposed not only to various infections but also to other substances of extrinsic origin.[†]

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† Since the original observations of Metchnikoff and those of subsequent workers were made of necessity upon the fate of particulate matter, the phenomenon of phagocytosis is generally considered as occurring only with materials of easily discernible physical structure. Particulateness, arbitrarily defined, is a condition of matter with the characteristic of visible dimensions, microscopic or otherwise. Phagocytosis may conceivably be incited by substances of molecular size, too minute to be visible or to be accepted as "particulate." Most

These extrinsic substances are considered nonpathogenic for the general population, since no ill effects are noted from exposure to them. Such particulate matter as the pollen of the inspired air and the food ingested is without disturbing results, and upon invading the tissues of the average person may incite the normal phagocytic response with its scavenging mechanism, but does not appear to stimulate to action the immune response, resulting in profound alteration of the cell contents, with conversion of normal globulin to antibody globulin and the invoking of the antibody-antigen reaction typical of allergy.²

In a small proportion of the population, however (not over 10 per cent), such an effect seems readily elicited by even minute amounts of the foreign substance. A trace of pollen, a whiff of horse dander, a nut crumb, may cause an overwhelming antigen-antibody response, even to the point of danger to life. In the family history of such persons, clinical allergic conditions such as hay fever and asthma can be traced in many members and many generations.^{3, 4, 5} The trait seems to be governed by the Mendelian laws of heredity, and is discovered at an earlier age and in a greater number of children in those families where both parents have been found to be allergic.⁴ The clinical form of the allergy in any involved person is not itself inherited; an asthmatic parent may produce a child with hay fever, but the tendency to allergy is transmitted, the capacity of the cells to become sensitized upon exposure to a foreign substance. The best understood forms of clinical allergy—hay fever, asthma and urticaria—are characterized by this inherited ability to react allergically on normal exposure to small amounts of substances considered not generally irritating.

The greater proportion of the population may at times exhibit allergic responses which can only be called physiologic,⁶ since they may involve almost everyone. In such instances an important requirement for such antigen-antibody response is the exposure of the individual to massive, excessive doses of a protein. The inherited capacity for sensitization is not usually demonstrable. An example is the individual presenting no clinical history of allergy, personal or familial, who nevertheless develops severe general symptoms of serum sickness following the administration of heterologous serum. No inherited capacity to sensitization is evident in this person but the reaction may develop due to overwhelming exposure of the cells to the foreign substance. Approximately 90 per cent of the population can thus become sensitized to horse serum.⁷ Other instances are the severe general responses which may follow the administration of such biologic materials as liver extracts, insulin, toxoids and penicillin. These reactions are not well understood, and may in some cases be due to the overwhelming exposure of the cells to a foreign substance which may have been rendered more completely antigenic by linkage with some type of body protein.

studies of the phenomenon have been made upon material parenterally injected, although it may well enter the organism through other portals, such as the bronchial and gastrointestinal mucosa and the skin.

In other instances, the development of the antibody-antigen response is associated with neither the inherited capacity to sensitization nor the use of large amounts of antigen, but rather with the exposure of the organism to an antigen with an extremely high sensitizing potential, as in certain forms of dermatitis. Contact dermatitis, which apparently involves a very different type of sensitizing agent, may occur in the great majority of the population to essential oils, drugs, dyes and chemicals. At least 70 per cent of individuals exposed to the oleoresins of poison ivy,⁸ and 100 per cent of those exposed to those of primula,⁹ develop such a sensitization. The great proportion of the population may thus become clinically allergic, provided the surface exposure of the skin to the sensitizing agent be sufficient.

Whether the clinical sensitiveness of the individual be the result of (a) an inherited trait; (b) an overwhelming contact with the antigen, or (c) an exposure to antigen with high sensitizing value, the reaction represents an intense defensive effort of the individual against the invading antigen. The reticuloendothelial cell, originally phagocytic only, would appear to over-compensate, providing antibody in excessive amounts and leading to extensive antibody-antigen union, with consequent disturbing effects upon the allergic person. It is this specifically altered reactive capacity of the cell to the invading antigen, both viable and nonviable, that is the feature characteristic of all forms of clinical allergy and permits a classification as here submitted, even though the presence or the identity of the specific antibody in many instances has not been determined (table 1).

The clinically allergic individual can most readily be recognized as a skin sensitive type or a skin negative type according to his behavior upon skin test. Cooke⁶ has pointed out that the former type experiences an immediate reaction upon contact with the specific excitant, the latter a delayed.

It is apparent from the table that the skin testing procedure, considered by many as the preëminent diagnostic tool in allergic conditions, is actually useful in only a portion of the cases, those of the skin sensitive or wheal type, with an immediate reaction time of four hours or less between exposure of the allergic person to the antigen and the development of symptoms. The majority of these cases fall into the first subdivision, where the symptoms are spontaneous, linked often with hereditary influences. The child rendered promptly asthmatic upon contact with a horse, or developing immediate gastroenteritis upon ingestion of egg, is an example. The skin test, with the extract of the eliciting agent placed in intimate contact with the superficial skin cells by the scarification or by the intradermal method, becomes actively positive, the irregularly outlined wheal with itching and with a surrounding zone of erythema developing within a few minutes.

The positive skin test itself is an immediate allergic response, which is thought identical in mechanism with that which produces the clinical symptoms in the patient with an immediate type of allergy, whether spontaneous

TABLE I
The Clinical Forms of Allergy

I. Skin Sensitive or Wheal Type (Immediate Reaction Type)

a. Hereditary: Spontaneous

Allergic coryza, seasonal (hay fever), nonseasonal; bronchial asthma.

Causes: pollens; dusts; fungi; other airborne substances; foods.

Antibodies: skin sensitizing (histamine releasing); blocking (not histamine releasing).

Urticaria; angioedema of skin or alimentary tract; allergic headache; allergic nerve disorders.

Causes: foods.

Antibodies: skin sensitizing (histamine releasing); blocking (not histamine releasing).

b. Nonhereditary: Induced, Anaphylactic

Serum sickness, therapeutic accidents.

Causes: heterologous serum; antibiotics; organ extracts; toxoids; virus vaccines (egg media); helminths; (drugs as sulfa, mercury?).

Antibodies: skin sensitizing (histamine releasing); blocking (not histamine releasing); precipitating; muscle sensitizing (histamine releasing).

2. Skin Negative or Nonwheal Type (Delayed Reaction Type)

a. Noninfective:

Hereditary:

Allergic coryza; bronchial asthma; urticaria; angioedema of skin or alimentary tract; dermatitis; allergic headaches; allergic nerve disorders.

Causes: foods; some drugs.

Antibody: not known.

Nonhereditary:

Contact dermatitis.

Causes: natural and synthetic oils; resin; chemicals; drugs; foods.

Antibody: cellular, dermatitis producing, transferable in reticuloendothelial cells (not histamine releasing?).

Drug allergy.

Causes: arsenic; quinine; barbiturates; iodides; aspirin.

Antibodies: not known.

b. Infective:

Hereditary:

Allergic coryza; bronchial asthma; urticaria; angioedema of skin or alimentary tract; dermatitis; sinusitis.

Causes: bacterial and fungus products.

Antibody: not known.

Nonhereditary:

Tuberculin type sensitization; periarthritis; vascular allergy; rheumatoid arthritis.

Causes: bacterial products.

Antibody: not known except for tuberculin cellular type transferable in reticuloendothelial cells and leukocytes (not histamine releasing).

or induced. The antigen, such as pollen bodies, dust granules, animal danders or food substances, whether inhaled or ingested in a particulate form, or injected in a soluble extract form, reacts in the tissues with the skin sensitizing antibody, an immune substance characteristic of the wheal type of allergy.

The skin sensitizing antibody is essentially a human antibody, although occasionally found in the lower animal.¹⁰ It was so named because its presence can be demonstrated readily only by the direct or indirect skin test. In the direct skin test, the antigen (introduced by intracutaneous or scratch

technic) combines with the skin sensitizing antibody in the allergic individual's skin and produces the typical elevated wheal with surrounding erythema. This skin sensitizing antibody is also present in the serum of allergic patients, and its presence is demonstrated by injecting such serum into skin sites of a normal person. When these sites are tested with the specific antigen, the typical wheal and erythematous reaction characteristic of antigen-antibody reaction with histamine release is observed.¹¹ Skin areas in a nonallergic thus treated with skin sensitizing antibody from a ragweed hay fever patient can be shown to react to ragweed antigen in a manner similar to those in the allergic patient. Such antibody shows its presence, not by any precipitin effect in the test tube when mixed with antigen, or any appreciable effect upon the lower animal, but only through its capacity to interact with antigen to release histamine (a) from the allergic human cell, as in the wheal producing skin test; (b) from the allergic human cell, as in in vitro mixtures with untreated ragweed patient's blood¹²; (c) from the normal human cell, as in the indirect test, and (4) from cells of the normal lower animals,¹³ when they are exposed to mixtures of skin sensitizing antibody and antigen incubated in vitro. This antibody has the characteristic of being thermolabile,¹⁴ being completely destroyed at 56° C. within five hours. It usually provides an accurate index of the degree of clinical sensitiveness, a condition which varies from patient to patient. Since in highly allergic individuals its concentration is greater, the wheal response upon test is more intense. This finding is used to advantage in estimating dosage of specific injections, especially of pollen extracts. The functions of the skin sensitizing antibody are not thoroughly understood. After many years of intensive specific immunizing therapy, its concentration in the patient's serum is apparently decreased, but not after one or two years of treatment, when often it was actually increased,¹⁵ even though the patient obtains excellent clinical results.

While the skin sensitizing antibody usually is considered to occur spontaneously, there are instances where it has been shown to have been induced. For instance, it may on occasion be found in the serum of the anaphylactic animal which has been subjected to massive doses of antigen. Cooke and Spain¹⁶ showed that passive transfer sites made in the skin of a normal individual with anti-eggwhite rabbit serum may react, upon test with egg-white, with the immediate wheal and flare response indicative of the presence of the skin sensitizing antibody. This type of antibody may also be induced in normal man by injection of such foreign protein as horse serum, liver extract and other biologic agents.¹⁶ Skin sensitizing antibodies to the extracts of the helminths may result from injection into the normal man of the specific extracts, as of ascaris.¹⁷ In the parasitic helminth infestations, such as schistosomiasis, echinococcus disease, trichinosis, filariasis and ascaris infestation, where the organism has been invaded clinically by massive quantities of a foreign nonbacterial protein, the immediate wheal type of skin re-

sponse, indicative of the presence of the skin-sensitizing antibody, is found upon skin test of the host with extracts of the parasite involved, while the anaphylactic type of antibody can also be found in the serum.¹⁸ DuBois, Schloss and Anderson¹⁹ have shown that temporary cutaneous hypersensitivity to the specific protein was induced in 50 per cent of normal infants following the initial intestinal absorption of the food protein. In allergic individuals nonsensitive to grass pollen extract, skin sensitizing antibodies to this antigen could be produced by Fitzgerald and Sherman²⁰ upon injecting massive amounts of grass pollen extract.

Histamine, which is normally present in a bound form in many tissues, as emphasized by Code,²¹ is released by the union of antigen and skin sensitizing antibody and has a pronounced cell damaging effect. It can produce capillary permeability, disturbing the equilibrium between the capillary blood pressure and the osmotic tissue pressure. The resulting flow of plasma into the tissues causes edema, the temporary pathologic finding typical of the wheal form of allergy. For instance, in hay fever such an edema occurs in the tissues of the upper respiratory tract, in bronchial asthma in the tissues of the lower respiratory tract. The pattern of symptoms, hence the form of the clinical condition, is determined by the site of the edema, which is apparently also the site of the greatest antigen-antibody union.

The skin sensitizing antibody is not to be confused with another antibody, discovered by Cooke and his associates²² in the serum of hay fever patients who had been adequately treated with their specific pollen extracts, and subsequently also found in nonallergic persons²³ who had received large experimental pollen injections. The importance of this immune substance, termed the blocking antibody, remains obscure. As in the case of the skin sensitizing antibody, the blocking antibody cannot be demonstrated by the appearance of precipitin in the test tube when such blocking antibody is mixed with antigen, nor by any demonstrable sensitizing effect of the antibody-containing serum upon the lower animal. However, if antigen is not present in excess, this immune antibody is able to interfere with the usual union of antigen and skin sensitizing antibody which ordinarily leads to histamine release.¹³ The presence of histamine is usually shown by (1) its ability to produce a wheal when injected into the normal human skin, (2) by a sharp contraction of the smooth muscle strip of the normal lower animal exposed to it, or (3) by chemical estimation of $\text{N}\alpha$ -(2, 4 dinitrophenyl) histamine. By none of these tests can histamine be demonstrated if the antigen in proper proportions be incubated with the skin sensitizing antibody in the presence of the blocking antibody. For instance, incubated in vitro mixtures of antigen, such as ragweed and blood from a treated ragweed hay fever patient containing blocking antibody as well as skin sensitizing antibody, fail to show evidences of histamine release by the three methods mentioned, provided the antigen be present not in excess but in concentrations just sufficient to be neutralized by the blocking antibody.¹³ The antigen in such tests is in an amount just

sufficient to cause a maximal response when combined with serum containing skin sensitizing antibody alone, but a negative response when blocking antibody is present. If excess antigen be then added to such a mixture of antigen, skin sensitizing antibody and blocking antibody, after all of the blocking antibody has united with the antigen, the excess antigen will then react with the less avid skin sensitizing antibody to release histamine. This indicates that the blocking antibody, due to its induced formation by antigen injection, has a greater avidity for antigen than does the skin sensitizing antibody (a conclusion also reached by Cooke⁸ in his studies of the whealing properties of such mixtures), and that the blocking antibody and the antigen combine without histamine release.

In the second subdivision of the skin sensitive or immediate type of clinical allergy, the clinical symptoms are induced. This subdivision is represented by serum sickness. The skin sensitizing antibody is present, having been induced in the patient's skin, which was negative upon test to horse serum before exposure to it but which now reacts positively upon test after the development of serum sickness. Passive transfer to a normal skin of the serum sensitiveness can easily be accomplished.¹⁰ These findings indicate that the skin sensitizing antibody can be produced physiologically in the normal person. Such skin sensitizing antibodies remain for many years and are thought responsible for the prompt, even violent reactions which may occur upon subsequent reinjection of horse serum. In addition there are, in serum sickness, features comparable to those found in the lower animal rendered artificially sensitive or anaphylactic.¹⁰ Following the injection of antitoxin there is usually an incubation period of seven to 10 days within which the individual, previously nonallergic to horse serum, suffers joint pains, urticaria, gastrointestinal symptoms, headache, malaise and fever, evidences of an accomplished sensitization. At this time there are demonstrable in his serum antibodies otherwise found only in the anaphylactic animal.¹⁰ Precipitin can be shown in *in vitro* mixtures of the serum with the antigen horse serum; also, antibodies can be shown which are able, through injection of this serum into a normal animal, to confer horse serum sensitization especially demonstrable upon the smooth muscle, as shown by violent contraction due to the histamine releasing union of the antibody and antigen.

Allergic accidents due to injections of penicillin, liver extracts, toxoids, virus vaccines prepared with egg media, and other biologic agents usually containing protein, are grouped with serum sickness, since they cause similar clinical and anaphylactic effects. Skin sensitizing and anaphylactic antibodies are less often demonstrated, due probably to the usually smaller quantity of injected material. Skin sensitizing antibodies have occasionally been induced by drugs such as phthalic anhydride, as in Kern's case,²⁴ and by the sulfa group and mercury. Leftwich²⁵ demonstrated positive wheal responses in individuals sensitive to sulfonamides when they were tested with

sera from nonallergic persons with high sulfonamide blood levels due to intensive sulfonamide therapy. Gelfand²⁶ and Weisman and Gelfand²⁷ demonstrated positive immediate reactions in persons sensitive respectively to the mercury compounds, Mercuhydrin and Mercaptomerin by testing with sera obtained from cases clinically treated with these drugs. Not only with such serum conjugates have skin responses been elicited but also occasionally with the drug itself. Sherman and Cooke²⁸ showed the presence of a positive skin sensitizing antibody to sulfadiazine in a patient clinically sensitive to the drug and were able to transfer it, using the serum, to the skin of a normal person. Other investigators, Whittemore and de Gara,²⁹ Gottlieb³⁰ and Goodman and Levy,³¹ have obtained similar results with the sulfa drugs.

In the second major group of clinical allergic conditions, those of the skin negative, nonwheal type, the symptoms are delayed for four to 24 hours or more following contact with the antigen. The positive skin test cannot be demonstrated, nor should it logically be expected. In the first subdivision of this group, the noninfective hereditary type, the symptoms are due usually to foods by ingestion, but at times may be due not to the food protein itself but to some digestive products, as in the patient described by Cooke,³² who had a positive clinical history of allergy to milk but negative skin tests to it. When the proteose fraction was tested, however, immediately positive skin responses were obtained.

In many delayed cases with negative skin reactions, however, the question arises as to whether some mechanism is involved other than the histamine releasing, wheal producing type. Certainly in the nonhereditary forms of dermatitis due to contact with plant oleoresins, drugs and chemicals, there is evidence to show that, while no histamine producing mechanism may be shown, the cells of the reticuloendothelial system, especially those of the spleen and lymph nodes, contain the sensitizing antibody. Normal guinea pigs could be sensitized by Crepea and Cooke³³ to poison ivy extract by injecting into the peritoneum of the normal animal* the lymphoid and reticuloendothelial cells of the spleen as well as serum obtained from sensitized pigs according to a technic similar to that employed by Chase³⁴ in transferring tuberculin sensitiveness.

Allergic symptoms, usually delayed, may follow the administration of such drugs as arsenic, quinine, the barbiturates and the iodides. No constantly reliable tests other than the clinical are available. Aspirin in 5 gr. doses may produce serious, even lethal effects, usually in patients suffering from infective types of asthma. The symptoms are immediate, yet the skin test is negative. The mechanism is unknown.

The second subdivision of the skin negative or nonwheal type contains

* The normal animals, however, had been patch tested with poison ivy extract 24 hours before being subjected to sensitization. As pointed out by Grodnick in his discussion of this study, sensitization could conceivably be induced by the patch test, which is known to initiate sensitization, although usually after a longer incubation period than 24 hours.

the clinical allergic conditions considered due to bacterial activity. In such infective forms of allergy the sensitization appears to result from exposure to the growth of organisms usually located in the paranasal sinuses or in the lymphoid tissues of the nasopharynx. While it has been shown that a hereditary feature³³ is often present, as in coryza and bronchial asthma due to bacterial activity, the mechanism is unknown, the antibody yet to be demonstrated. That specific sensitization is present, however, is suspected from the behavior of such cases when exposed to their own bacterial products in an autogenous vaccine prepared from organisms cultured from tissue sections of tonsils, adenoids or sinus mucosa removed at operation, and occasionally from sinus washings. With very high dilutions of such vaccines, pronounced local reactions with erythema, swelling, local temperature, and induration often appear at the site of the injection at the end of 24 hours, even with intracutaneous doses of 0.05 to 0.1 ml. of a 1-10,000 or 1-1000 dilution of the usual 1.0 per cent by volume heatkilled vaccine. There may also occur constitutional symptoms, characterized by fever, chills, joint pains and stubborn asthma, even status asthmaticus, which may persist for days or weeks, in spite of all efforts to control it.

The tuberculin type of allergy is nonhereditary and results from a sensitization to the growth products of organisms with which the individual has been infected. A 24 to 48 hour delayed inflammatory response may be demonstrated upon skin test with the bacterial products. In this group occur brucellosis, tularemia, glanders, typhoid fever, fungus infections and lymphogranuloma venereum,⁶ in all of which a positive skin reaction may be elicited as indicative of active infection, present or past. Such reactions would seem to involve a specific antibody of definitely cellular type. Chase³⁴ has been able to sensitize normal guinea pigs by injecting washed cells from the spleen, lymph nodes and peritoneal exudates of tuberculin sensitive animals. Lawrence³⁵ has shown that a similar mechanism exists in man, since he was able to transfer tuberculin sensitiveness to skin sites in the normal by using washed leukocytes from a tuberculin positive individual.

Periarteritis is considered a sensitization effect^{37, 38, 39} and has been observed by many to occur in allergic persons, particularly those suffering from asthma who have received large doses of sulfonamides or therapeutic sera. Rich³⁷ has reported that the administration of such agents also has been followed by arteritis, with localized hyaline and fibrinoid degeneration of the media with perivascular infiltration. He suggested that such specific sensitization was caused by an eliciting agent, probably a hapten, which was formed by attachment of the drug, such as the sulfonamide, to the plasma proteins. Similar pathologic changes have been produced by him in rabbits with large injections of foreign serum. Other vascular diseases considered allergic^{40, 41} are disseminated lupus, scleroderma, dermatomyositis, rheumatic fever and rheumatoid arthritis, the so-called collagen diseases. The allergic mechanisms in this group are obscure.

In human glomerulonephritis, Lange⁴² and his associates have presented

evidence to show that this condition is characterized by an organ specific antigen-antibody reaction, demonstrable in 73 per cent of tests done upon patients in all stages of the disease. The specific antibody is said to be present constantly. Spain, Fontana, and De Sanctis⁴³ have found that in the majority of 18 children suffering from nephrosis there were positive familial and personal histories of clinical allergic conditions such as hay fever, allergic coryza and bronchial asthma, and positive intracutaneous tests with such respiratory excitants as dusts and animal danders. Such observations indicate a linkage between the kidney pathology and the sensitized cell reaction. There is need for further investigations of such types of antibody responses.

BIBLIOGRAPHY

1. Frances, T., Jr.: Response of the host to the parasite, in Dubos, R. J.: *Bacterial and mycotic infections of man*, 1948, J. B. Lippincott, Philadelphia, pp. 90-109.
2. Cannon, P. R.: Antibodies and the protein reserve, *J. Immunol.* **44**: 107, 1942.
3. Cooke, R. A., and VanderVeer, A.: Human sensitization, *J. Immunol.* **1**: 201, 1916.
4. Spain, W. C., and Cooke, R. A.: Studies in specific hypersensitiveness. II. The familial occurrence of hay fever and bronchial asthma, *J. Immunol.* **9**: 521, 1924.
5. Adkinson, J.: The behavior of bronchial asthma as an inherited character, *Genetics* **5**: 363, 1920.
6. Cooke, R. A.: Immunology of allergy, *Am. J. Med.* **3**: 523, 1947.
7. Mackenzie, G. M.: In *Cecil's Textbook of medicine*, 7th Ed., 1947, W. B. Saunders Co., Philadelphia, p. 545.
8. Spain, W. C.: Studies in specific hypersensitiveness. VI. *Dermatitis venenata*, *J. Immunol.* **7**: 179, 1922.
9. Block, B., and Steiner-Wourlisch, A.: Die willkürliche Erzeugung die Primelüberempfindlichkeit beim Menschen und Ihre Bedeutung für das Idiosynkrasieproblem, *Arch. f. Dermat. u. Syph.* **152**: 283, 1930; quoted by Chase, M.: The allergic state, in Dubos, R. J.: *Bacterial and mycotic infections of man*, 1948, J. B. Lippincott, Philadelphia, p. 146.
10. Cooke, R. A., and Spain, W. C.: Studies in specific hypersensitiveness. XXXVI. A comparative study of antibodies occurring in anaphylaxis, serum disease and in the naturally sensitive man, *J. Immunol.* **17**: 295, 1929.
11. Prausnitz, C., and Kustner, H.: Studien über die Überempfindlichkeit, *Centralbl. f. Bakt.* **86**: 160, 1921.
12. Katz, G., and Cohen, S.: Experimental evidence for histamine release in man, *J. A. M. A.* **117**: 782, 1941.
13. Spain, W. C., Strauss, M. B., and Neumann, E.: In vitro release of histamine by hypersensitive (allergic) serum in contrast to immune (treated) serum in antigen and normal rabbit blood mixtures, *J. Allergy* **21**: 318, 1950.
14. Loveless, M. H.: Immunologic studies of pollerosis. I. The presence of two antibodies related to the same pollen antigen in the serum of treated hay fever patients, *J. Immunol.* **38**: 25, 1940.
15. Sherman, W. B.: Changes in serological reactions and tissue sensitivity in hay fever patients during the early months of treatment, *J. Immunol.* **40**: 289, 1941.
16. Sherman, W. B.: Drug allergy, *Am. J. Med.* **3**: 593, 1947.
17. Brunner, M.: Active sensitization in human beings, *J. Allergy* **5**: 257, 1934.
18. Chase, M. W.: Allergic inflammation, delayed response, in Dubos, R. J.: *Bacterial and mycotic infections of man*, 1948, J. B. Lippincott, Philadelphia, pp. 136-148.
19. DuBois, R. O., Schloss, O. M., and Anderson, H. F.: The development of cutaneous hypersensitivity following the intestinal absorption of antigenic protein, *Proc. Soc. Exper. Biol. and Med.* **23**: 176, 1925.

20. Fitzgerald, J. D., and Sherman, W. B.: The specificity of blocking antibody induced by grass pollen extracts, *J. Allergy* **20**: 286, 1949.
21. Code, C. F.: Histamine in blood, *Physiol. Rev.* **32**: 47, 1952.
22. Cooke, R. A., Barnard, J. H., Hebard, S., and Stull, A.: Serological evidence of immunity with coexisting sensitization in a type of human allergy, *J. Exper. Med.* **62**: 733, 1935.
23. Cooke, R. A., Loveless, M. H., and Stull, A.: Studies on immunity in a type of human allergy (hay fever): serologic response of non-sensitive individuals to pollen injections, *J. Exper. Med.* **66**: 689, 1937.
24. Kern, R.: Asthma and allergic rhinitis due to sensitization to phthalic anhydride, *J. Allergy* **10**: 164, 1939.
25. Leftwich, W. B.: An intradermal test for the recognition of hypersensitivity to the sulfonamide drugs, *Bull. Johns Hopkins Hosp.* **74**: 26, 1944.
26. Gelfand, M. L.: Hypersensitivity to Mercuhydrin with positive skin test to post-treated Mercuhydrin serum, *J. Allergy* **20**: 404, 1949.
27. Weisman, L., and Gelfand, H. H.: Mercaptomerin sensitivity, report of a case, *J. A. M. A.* **147**: 1559, 1951.
28. Sherman, W. B., and Cooke, R. A.: Sulfadiazine sensitivity with demonstrable skin-sensitizing antibody in the serum, *Am. J. Med.* **2**: 588, 1947.
29. Whittemore, A. L., Jr., and de Gara, P. F.: Sulfadiazine sensitivity: an unusual case with successful passive transfer, *J. Allergy* **18**: 382, 1947.
30. Gottlieb, P. M.: Sensitivity to mercurial diuretics: report of a case of urticaria due to Mercupurin, *Ann. Allergy* **6**: 518, 1948.
31. Goodman, M. H., and Levy, C. S.: Development of cutaneous eruption during administration of sulfanilamide, *J. A. M. A.* **109**: 1009, 1937.
32. Cooke, R. A.: Protein derivatives as factors in allergy, *Ann. Int. Med.* **16**: 71, 1942.
33. Crepea, S. B., and Cooke, R. A.: Study on the mechanism of dermatitis venenata in the guinea pig with a demonstration of skin sensitizing antibody by passive transfer, *J. Allergy* **19**: 353, 1948.
34. Chase, M. W.: The cellular transfer of cutaneous hypersensitivity to tuberculin, *Proc. Soc. Exper. Biol. and Med.* **59**: 134, 1945.
35. Cooke, R. A.: Infective asthma: indications of its allergic nature, *Am. J. M. Sc.* **133**: 309, 1932.
36. Lawrence, H. S.: The cellular transfer of cutaneous hypersensitivity to tuberculin in man, *Proc. Soc. Exper. Biol. and Med.* **71**: 516, 1949.
37. Rich, A. R.: The role of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy, *Bull. Johns Hopkins Hosp.* **71**: 123, 1942. *Ibid.*: Additional evidence of the role of hypersensitivity in the etiology of periarteritis, *Bull. Johns Hopkins Hosp.* **71**: 375, 1942.
38. Gelfand, M. L., and Aranoff, S.: Periarteritis nodosa—possible relation to the increased usage of the sulfonamides, *Ann. Int. Med.* **30**: 919, 1949.
39. Wilson, K. S., and Alexander, H. L.: The relation of periarteritis nodosa to bronchial asthma and other forms of hypersensitivity, *J. Lab. and Clin. Med.* **30**: 195, 1945.
40. Rich, A. R.: Hypersensitivity in disease with especial reference to periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus and rheumatoid arthritis, Harvey Lectures, 1946-47, p. 106.
41. Kampmeier, R. H.: Vascular diseases due to hypersensitivity—so-called diffuse collagen disease, *Am. Pract. and Digest. Treat.* **1**: 113, 1950.
42. Lange, K., Weiner, D., Gold, M. M. A., Tchertkoff, V., and Simon, V.: Autoantibodies in different phases of human glomerulonephritis, *Bull. New York Acad. Med.* **25**: 447, 1949.
43. Spain, W. C., Fontana, V. J., and De Sanctis, A.: To be published.

IRON METABOLISM: CLINICAL EVALUATION OF IRON STORES*

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IN 1948 Rath and Finch¹ described a simple method for the estimation of the iron stores in man by examining an unstained smear of bone marrow aspirate. In the present paper the method is applied to a large cross section of hematologic problems. The data obtained indicate that marrow examination for hemosiderin is a reliable index of iron stores in man and is frequently the decisive test in the diagnosis of anemia due to iron deficiency.

MATERIAL AND METHODS

Two hundred ninety-eight marrow examinations were made on consecutive patients at the King County Hospital referred for hematologic evaluation between September, 1949, and December, 1951, and on a small group of patients and normal subjects at the University of Washington School of Medicine. Of the entire group, 31 had completely normal blood findings, some being healthy students and laboratory workers and the rest patients in whom hematologic disease was excluded. Seventy-three patients had iron deficiency anemia. The mean cell volume was less than 80 cubic micra in 41 of the 50 patients in whom indices were determined. Of 43 with serum iron determinations, 39 were less than 70 micrograms per 100 ml. of serum (normal range, 80 to 150 μ). Fifty-eight patients were uncomplicated, with typical laboratory findings of iron deficiency and a response to iron therapy in the 55 patients who were adequately followed.

Fifteen individuals had iron deficiency anemia complicated by other conditions, such as infection. Forty-six patients had anemia associated with infection. Twenty patients had cirrhosis with enlarged liver, altered liver function tests and frequently a history of alcoholism, of whom three had a diagnosis of hemochromatosis made by liver biopsy. Twenty-five patients had untreated pernicious anemia, on the basis of a macrocytic anemia, megaloblastic marrow, absence of free hydrochloric acid in gastric juice, and response to liver or vitamin B₁₂ therapy. Thirty patients had malignant disease without evidence of blood loss. Nine had uremia, with a blood urea nitrogen over 50 and a moderate to severe anemia, two of whom had associated loss of blood. Twelve patients had hemolytic anemia, the increased hemoglobin catabolism being confirmed by studies of fecal urobilinogen output. Patients

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with other miscellaneous conditions are also included, most of them associated with anemia. Less than 5 per cent of the patients were children. The difficulty of obtaining adequate marrow tissue from small children makes this technic less useful in the first few years.

Marrow was aspirated with a short-beveled 14-gauge needle, usually from the sternum but occasionally from the lumbar spines or iliac crest. The first few drops were smeared immediately. About 3 ml. of mixed blood and marrow were then withdrawn into an equal volume of 4 per cent sodium citrate. The mixture was placed in a large watch glass where the marrow particles could be identified, removed and smeared on cover glasses. In addition to the smears stained with Wright-Giemsa, at least one smear containing adequate marrow particles was mounted unstained and examined for hemosiderin granules. Under low-power magnification and with reduced illumination, an area of marrow tissue was identified by the characteristic appearance of the reticulum and fat cells, and the relative absence of mature erythrocytes. Such a low-power search for a suitable field is of prime importance, for the hemosiderin granules are not found in areas of marrow cells diluted in blood. Under oil immersion, magnification approximately 1,000, the hemosiderin appears as golden-yellow, refractile granules, varying from a fraction to several micra in diameter.

Marrow iron can be clearly identified with the Berlin blue stain.* Such preparations were made in many instances including most of the patients with iron deficiency. In general, when iron was present the stained smear appeared slightly more laden with granules than the unstained. Only very rarely did staining reveal iron in a marrow thought to be free from iron without it. When practice was obtained in examining the unstained preparations, the staining was found to be unnecessary. For the purpose of this report, only observations on unstained material are reported.

The iron content of the marrow smears was graded by a simplification of the method of Rath and Finch.¹ The same terminology and grading numbers have been employed, but all marrows have been placed into four categories for this report:

{ 0	None
trace	Very rare granule
{ 1	Very slight
2	Slight
{ 3	Moderate
4	Moderately heavy
{ 5	Heavy
6	Very heavy

* 4 gm. of potassium ferrocyanide diluted to 20 c.c. with water. Concentrated HCl added until a permanent white precipitate forms. Filter, and cover smears with filtrate for 30 minutes. Use only glassware made iron-free by washing in dilute nitric acid.

RESULTS

Since the purpose of these observations is to indicate the usefulness of marrow examination for iron in the spectrum of hematologic problems, care has been taken in establishing specific diagnosis, particularly in respect to iron deficiency. Table 1 summarizes the distribution of marrow iron in different diseases. The miscellaneous group, in addition to containing pa-

TABLE I

Marrow Iron Content	0-Trace	1-2	3-4	5-6
Normal	4	21	6	
Iron Deficiency Uncomplicated	54	4		
Iron Deficiency Complicated	14	1		
Infection	6	12	20	8
Cirrhosis	4	10	1	5*
Pernicious Anemia	2	3	18	2
Nonbleeding Malignancy	1	16	13	
Uremia	1	2	6	
Hemolytic Anemia		3	5	4
Miscellaneous	10	20	18	4

* Three in this group had hemochromatosis.

tients with unusual diseases not worthy of separate cataloging, contains patients in whom the diagnosis was questionable.

The amount of iron present in a normal group of subjects was defined (table 1). Of 31 individuals, four had grade 0-trace, 21 had grade 1-2 marrow iron, and six were graded 3-4. Of the four individuals with little

RELATION OF MARROW IRON TO SEX

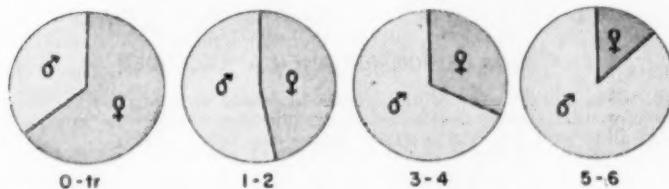


FIG. 1. The smaller iron stores in the female are demonstrated. All patients have been divided into four groups according to marrow iron content.

or no iron, two were young women in the menstrual age and two were children.

The difference in amount of stored iron between male and female subjects is shown in figures 1 and 2. This difference is reflected not only in the incidence of iron deficiency (21 male, 52 female) but also in the size of the stores in those patients not clinically iron deficient (figure 2). This

is presumed to reflect the iron losses of the female during menstruation and pregnancy.

Excluding iron deficiency anemia, there appeared to be a relationship between the size of the iron stores and the severity of anemia. Figure 3 is interpreted as reflecting a shift of iron from red cell mass to tissue stores as anemia develops.

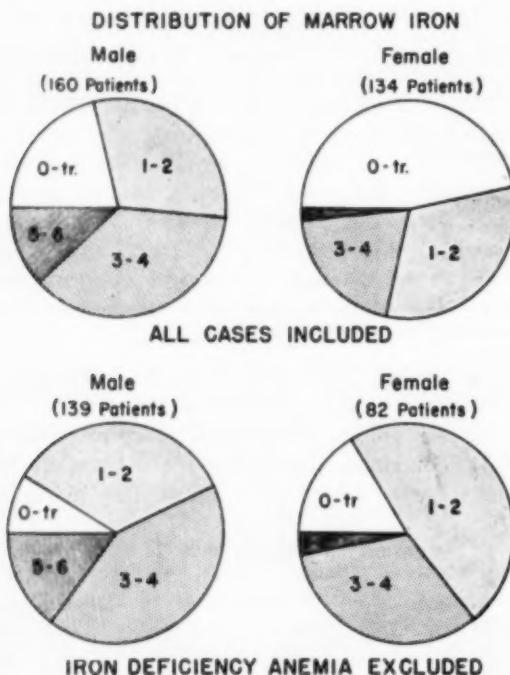


FIG. 2. Greater iron stores in the male as contrasted to the female are seen in both figures. *Above* the frequency distribution of marrow iron is separately graphed for each sex. *Below* all patients with iron deficiency anemia have been excluded.

In the total group of patients studied, no significant difference in the hemosiderin content of the marrow was seen with increasing age when the sex incidence of patients was taken into consideration.

There were 73 patients with iron deficiency anemia by the criteria listed above. The marrow iron in 68 patients was graded 0-trace and in five as grade 1-2 (table 1).

In 46 patients with infection of varying degree, the majority showed a definite increase in iron stores. In other disease states associated with anemia but no known blood loss, for example, cirrhosis, pernicious anemia,

HEMATOCRIT VS. MARROW IRON

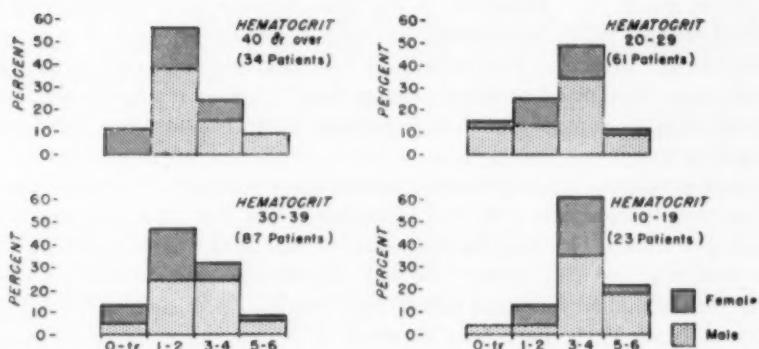


FIG. 3. Decreasing hematocrit levels were associated with increasing iron stores in both men and women. Patients have been divided into four groups according to hematocrit. All patients with iron deficiency anemia were excluded. Each marrow was graded according to its iron content on a scale of 0 to 6. The distribution of such grading is separately graphed for each group.

nonbleeding malignant lesions, uremia and hemolytic anemia, marrow iron was usually increased. Occasional instances of depleted marrow iron were found in these diseases, and in approximately half of these there was indication by other laboratory tests of iron deficiency. Although all of these patients were not treated with iron, those who were did not respond, indicating that iron depletion was not the primary cause of the anemia.

DISCUSSION

Iron is stored in the tissues as ferritin or hemosiderin. Only the latter form is visible microscopically. Quantitative measurements of tissue ferritin and hemosiderin have shown parallel changes of these two forms of storage iron, and isotope studies indicate that both forms are readily available for hemoglobin production.² These stores are found in greater concentration in the liver and reticuloendothelial system. The iron reserve as mobilized by phlebotomies in man has been found to be approximately 1,500 mg., although it must vary considerably among individuals.³

In the development of iron deficiency anemia, the earliest change is the contraction of the iron reserve. Clinical evaluation of this iron reserve should allow early detection of iron deficiency. The opportunity to examine iron content of the reticuloendothelial system is provided by marrow aspiration. No stain is needed to see the golden refractile hemosiderin granules, but it is most important that a piece of marrow tissue be examined, since few reticuloendothelial cells are seen among free marrow cells. Tissues from autopsy appear to give confusing results,⁴ but fixed sections of marrow aspirate may be satisfactory.⁵

Normal subjects usually have recognizable hemosiderin in their marrow (*trace* to grade 3). However, it has been demonstrated repeatedly that normal red cell values and serum iron may be associated with no marrow hemosiderin. Attempts to remove iron by phlebotomies in such a circumstance show little or no available storage iron.^{5,6} This represents the sub-clinical stage of iron deficiency, with depleted stores but no other manifestations of lack of iron.

As anticipated, in iron deficiency anemia there is usually a virtual absence of marrow hemosiderin (68 of 73 patients). In five patients there was grade 1-2 iron. This may be explained by the slower mobilization of the last portion of the iron stores.⁷ In both animals and man, following parenteral iron administration and subsequent bleeding, persistent large aggregates of hemosiderin have been observed at a time when impaired hematopoiesis due to iron deficiency existed. This was clearly the case in one of these five patients.

The differential diagnosis between the anemia of iron deficiency and infection is often difficult. Although serum iron is a sensitive index of iron deficiency, it is also depressed in infection and therefore is of little help in the differential diagnosis. Red cells may likewise show microcytosis in both. Hypochromia is usually more marked in iron deficiency anemia. In the patients reported here, a mean corpuscular hemoglobin concentration of 28 per cent or less (normal, 32 to 35 per cent) was found with one exception only in iron deficiency anemia. However, one third of iron deficient patients had a mean corpuscular hemoglobin concentration greater than 28, and this determination was of no assistance. Sternal marrow iron, however, changes in different directions in these two conditions. In infection there is a shift of iron from the red cell mass to stores as anemia develops, since appreciable iron cannot be excreted. In iron deficiency, iron is usually absent and never increased.

An attempt was made to estimate the value of marrow iron in diagnosis in 76 protocols of patients who were known to have had either iron deficiency or anemia of infection. On reviewing the records without marrow iron data, in 70 per cent of the cases clinical and laboratory information was considered adequate; in 26 per cent, additional information was essential for a definite diagnosis, and in 4 per cent an error in diagnosis would have been made without the marrow iron.

In thalassemia major and minor, in which the red cells closely resemble those of iron deficiency, marrow iron is also normal or increased.

These observations are convincing to us that marrow iron is the most dependable guide to the need for iron. Unless iron is reduced or absent in the marrow, a patient will not benefit from iron therapy.

SUMMARY

Iron stores were evaluated by direct examination of particles of aspirated marrow. Hemosiderin iron, when present, represents iron available for hemoglobin production.

In the normal individual, small amounts of hemosiderin are visible.

A striking difference in marrow iron is found between men and women.

In anemias other than those associated with blood loss, there is a shift of iron from red cells to tissue stores which is reflected in an increase in marrow hemosiderin.

In iron deficiency there is a virtual absence of marrow iron. Only those patients with a marked reduction or absence of marrow iron will respond to iron therapy. The anemia of infection may be clearly separated from iron deficiency anemia by examination of marrow iron.

BIBLIOGRAPHY

1. Rath, C. E., and Finch, C. A.: Sternal marrow hemosiderin, *J. Lab. and Clin. Med.* **33**: 81-86, 1948.
2. Shoden, N. A., and Finch, C. A.: Unpublished data.
3. Haskins, D., Stevens, A. R., Jr., Finch, S., and Finch, C. A.: Iron metabolism. Iron stores in man as measured by phlebotomy, *J. Clin. Investigation* **31**: 543-547, 1952.
4. Masshoff, W., and Gruner, P.: Das Eisen im punktierten Knochenmark, *Acta Haematologica* **5**: 19-29, 1951.
5. Hagen, P. S.: Personal communication.
6. Finch, S., Haskins, D., and Finch, C. A.: Iron metabolism. Hematopoiesis following phlebotomy. Iron as a limiting factor, *J. Clin. Investigation* **29**: 1078-1086, 1950.
7. Finch, C. A., Hegsted, M., Kinney, T. D., Thomas, E. D., Rath, C. E., Haskins, D., Finch, S., and Fluharty, R. G.: Iron metabolism. The pathophysiology of iron storage, *Blood* **5**: 983-1008, 1950.

HISTOPLASMOSIS, WITH REVIEW OF THE LITERATURE AND REPORT OF A CASE, PROVED BY CULTURE, WITH INVOLVEMENT OF THE UPPER LOBE OF EACH LUNG SIMULATING ACTIVE BILATERAL APICAL PULMONARY TUBERCULOSIS *

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FOLLOWING Darling's original description of histoplasmosis in 1906¹ from Panama and his subsequent communications regarding the same subject in 1908² and 1909,³ this disease was considered to be an extremely rare fatal tropical illness. Thereafter no report of a case of histoplasmosis was made in the medical literature until 1926, when Riley and Watson⁴ published their report of a case in a resident of Minnesota. Phelps and Mallory⁵ in the same year reported a case from Honduras.

It was Darling's impression that histoplasmosis was caused by a protozoan. This mistaken idea of the etiologic agent of this disease was corrected by DeMonbreun⁶ in 1934 when he succeeded in cultivating the organism from the spleen of an infant in Tennessee. This case, reported by Dodd and Tompkins,⁷ the first ever to be diagnosed before death, was recognized by finding numerous parasites in the large mononuclear cells on the stained blood film. Also, a blood culture taken two days before death was positive after an incubation period of about four weeks. DeMonbreun demonstrated by cultural methods that the causative agent was a fungus which grew in both a budding or yeastlike phase, as it appears in the diseased tissues, and in a mycelial phase. Conant⁸ and others have further reported in detail concerning the life cycle and the classification of the organism *Histoplasma capsulatum*. DeMonbreun, using monkeys, mice and puppies, was also the first investigator to reproduce the disease experimentally in laboratory animals. Tager and Liebow,⁹ using mice, and others employing rats, dogs, rabbits, guinea pigs, hamsters and chick embryos, have also successfully reproduced the disease. Infection and disease have been produced in laboratory animals by using either the mycelial or the yeastlike phase of the organism as the inoculum.

Because of the fact that, for years, all of the very few patients proved to have histoplasmosis had died either of or with this disease, it was considered that this illness was always generalized and was uniformly fatal. More recently it has been repeatedly shown^{10, 11, 12} that many individuals having

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both calcified pulmonary lesions and negative tuberculin reactions are sensitive to histoplasmin.

The suspicion that *H. capsulatum* frequently causes disease in man, aroused by finding a positive reaction to histoplasmin in many individuals with calcified lung lesions and negative tuberculin tests, was strengthened when case reports appeared by Bunnell and Furcolow¹⁸ and others showing that there was a benign form of histoplasmosis. This concept is continually being further amplified by reports of cases having cutaneous, mucosal,¹⁴ adrenal^{15, 16} and other forms of this disease. Recently it has been stated^{17, 47} that the generalized fatal infection, formerly considered to be the most frequent or the only form of histoplasmosis, is in reality the least common, while there are innumerable infections occurring without accompanying symptoms, and numerous cases with mild, more or less benign pulmonary and other illnesses.

The earlier reports concerning histoplasmin sensitivity in tuberculin-negative individuals with calcified pulmonary lesions,^{10, 11} and, later, communications by Furcolow, Mantz and Lewis¹⁸ and others describing patients with pulmonary infiltrates and mediastinal lymphadenopathy, also associated with histoplasmin sensitivity, were for the most part from those regions drained by the Mississippi River or its tributaries.

Geographic differences in sensitivity to histoplasmin have been shown by Palmer.¹⁹ White and Hill,¹² reporting studies made in the northeastern part of New York State, showed that in this region (which is the lifelong residential area of the patient whose case is reported below), disseminated pulmonary calcification was associated with skin sensitivity to histoplasmin in 94 per cent of a series of 114 cases. They also showed that in this same locality positive histoplasmin tests were found in 14.2 per cent of a control group of 305 individuals who did not have disseminated pulmonary calcifications.

Histoplasmosis is an infectious disease which can involve all of the tissues and organs of the body; and even though the yeastlike organisms are most frequently found in the cells of the reticuloendothelial system, this infection is not exclusively a disease of this system.^{9, 30, 50} Parenthetically, it has been suggested that the term reticuloendothelial cymycosis would be a more apt term for this disease.^{3, 6, 30} Regarding the presence of this fungus in the cells of the reticuloendothelial system, it has been stated that the organisms "affect,"⁴⁹ "invade,"⁹ "are primarily parasites of,"²⁸ or that "they are phagocytosed as a defense mechanism by"⁵⁰ these cells. In those cases coming to necropsy, the frequency of involvement of the lungs by *H. capsulatum* is second only to that of the lymph nodes, the liver and the spleen.^{16, 21} As concerns the pulmonary lesions in histoplasmosis, Darling in his original article¹ described "foci of catarrhal pneumonia and hemorrhages in the lungs," but further stated that ". . . the lungs play a very passive part, there being absolutely no leucocytic infiltration of the miliary

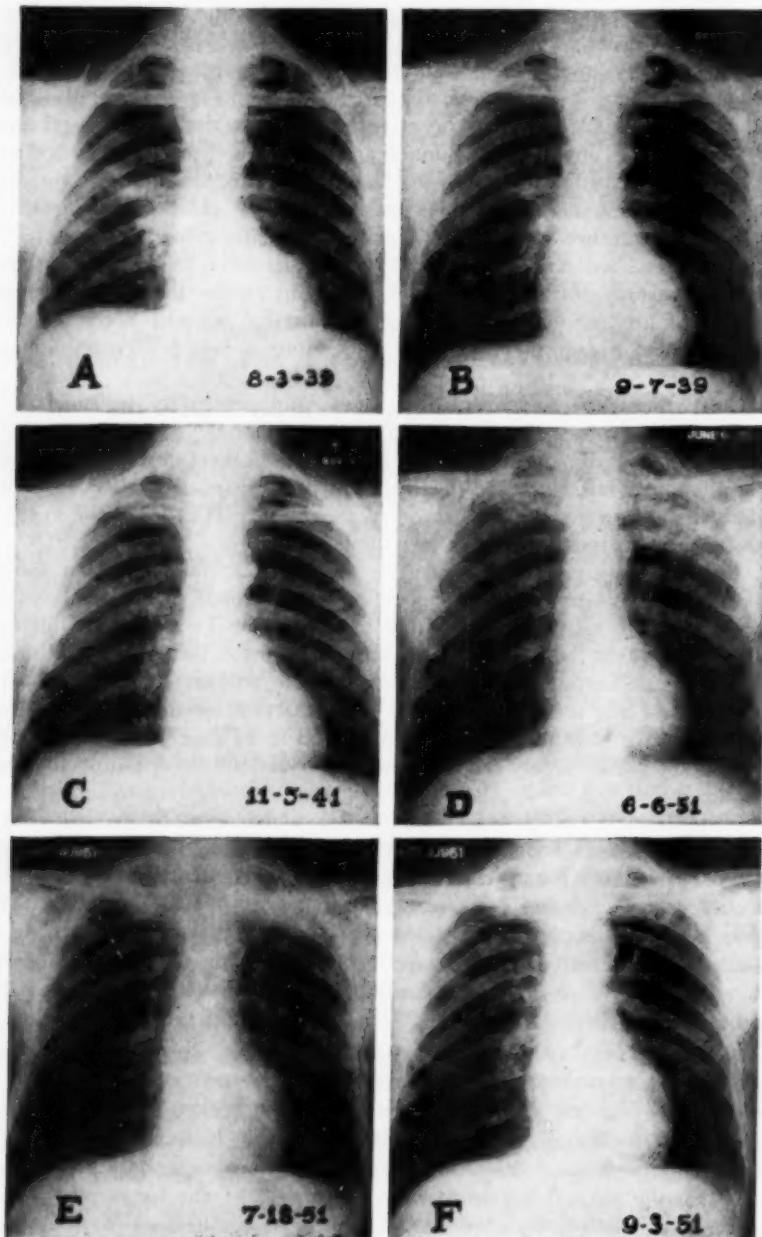


FIG. 1. *A*. Earliest film showing signs of bronchopneumonia on the right and small bilateral pleural effusions. *B*. Partial clearing of the pulmonary disease has occurred and evidence of pleural effusion on the right has disappeared. *C*. The lung fields are now clear;

pneumonic nodules." Histoplasmosis limited apparently to the lungs was described by Phelps and Mallory⁵ in 1926. Meleney,²⁰ reporting on pulmonary histoplasmosis in 1941, predicted that if this condition was kept in mind by clinicians and pathologists it would be found much more frequently. Hodgson, Weed and Clagett,²¹ in their recent paper on pulmonary histoplasmosis, stated that up to January 1, 1950, only 138 authenticated reported cases of histoplasmosis could be found, and that of this total number there was proved involvement of the lungs in only 65.

The following is an account of a case diagnosed at this hospital * as having bilateral upper lobe pulmonary histoplasmosis of mixed bronchopneumonic and cavitary types.

CASE REPORT

A 56 year old white male entered this hospital for the first time on July 15, 1951, complaining of moderate cough, the expectoration of 1.5 ounces of odorless mucopurulent sputum each day, wheezing in the chest, fatigue and anorexia of four months' duration, during which time he had lost 20 pounds in weight.

The present illness probably began in July, 1939, when he had a "hard cold," with fever as high as 104° F., chills, night sweats, marked cough with the expectoration of as much as 4 ounces of thick green sputum each day, and right sided pleuritic pain. Three weeks later, by which time he had improved markedly, he was referred for the first time to our out-patient clinic. He appeared ill, although the temperature was normal. Physical examination of the chest showed dullness to percussion over the lower part of the right lung and generalized bilateral rhonchi, most numerous and loudest on the right side. The chest roentgenogram (figure 1A) showed, in the middle third on the right, evidence of scattered areas of pulmonary disease of minimal extent without cavitation, small bilateral pleural effusions, calcified right hilar lymph nodes, and partial calcification of the aortic arch. The sputum was negative for tubercle bacilli by concentration. The diagnoses were: bronchopneumonia, right, minimal; bilateral pleural effusions, small; bronchitis, generalized.

Two subsequent out-patient clinic examinations were made at monthly intervals. The patient had continued to work. There had been no fever, but slight-to-moderate cough and expectoration had persisted. Physical examinations revealed no change. The chest roentgenograms (figure 1B) showed evidence of partial clearing of the right sided pulmonary and pleural disease. Two sputa were reported negative for tubercle bacilli. The diagnoses remained as before. He was improving.

The next examination was made two years later, in November, 1941. He had continued to work. There had been frequent colds associated with cough, expectoration, wheezing and bilateral mild pleuritic pain. He appeared to be in good general condition, and there was no fever. Physical examination revealed the presence of bilateral wheezing in the chest. The chest roentgenogram (figure 1C) showed that the signs of pulmonary and pleural disease on the right had completely cleared. Sputum was reported negative for tubercle bacilli. The diagnoses were: pulmonary disease of undetermined nature, minimal, right, recovered; bilateral pleural effusion, probably nontuberculous, cleared on the right, residual on the left; chronic generalized bronchitis.

He was not referred for reexamination until four years later, i.e., in December, 1945, at which time he reported that he had continued to work and that the above

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however, the left costophrenic angle remains blunted. D. Numerous areas of disease with cavitations have appeared in the upper half of each lung. E. Slight clearing on the right and slight-to-moderate clearing on the left have occurred. F. Evidence of very slight further clearing on each side is shown.

described symptoms had persisted. In addition, for the first time in his life, about 10 days previously he had had a moderate sized hemoptysis. The general condition was good and he was afebrile. Physical examination of the chest showed only a few bilateral marginal râles posteriorly. The chest roentgenogram showed, on comparison, no change, and the sputum was again reported negative for tubercle bacilli by concentration. The possibility of bronchiectasis was considered, and it was advised that a bronchogram be performed.

One and one-half years later, in April, 1947, he was referred for the advised bronchogram. Symptoms as above described had persisted, but there had been no further blood spitting. He had continued to work and had remained in fairly good general condition. There was no fetor oris, local or general enlargement of the lymph nodes or clubbing of the fingers. Physical examination of the chest showed diminished breath sounds and a few râles and rhonchi on the right. When the larynx, trachea and bronchi were being anesthetized it was noted that on the right true vocal cord there was a small smooth nodule covered with intact mucous membrane, but there were no laryngeal complaints. On comparison, the chest roentgenogram showed no change. The bronchogram, with satisfactory outlining of the right middle, the right lower, the left lingular and the left lower lobe bronchi, showed no abnormalities. No attempt was made to outline the bronchi of the right upper lobe or the remaining bronchi of the left upper lobe. The Mantoux test, his first tuberculin test, was positive.

At the next examination, four years later (June 6, 1951), he stated that he had continued to work and that, until three months earlier, there had been no change in the chronic complaints above listed and no further blood spitting. In March, 1951, he had caught a fresh chest cold which was followed for the first time in his entire life by persistent increased cough and expectoration, fatigue and anorexia, and within three months he had lost 20 pounds in weight. The general condition had deteriorated moderately. He was afebrile. Physical examination of the chest showed no changes. The chest roentgenogram (figure 1D), on comparison with the last previous film, taken approximately four years earlier, showed that numerous areas of pulmonary disease had appeared throughout the upper half of each lung, with signs of a moderate sized cavity in the upper third on each side. The presumptive diagnosis was active bilateral pulmonary tuberculosis, and it was recommended that he be admitted to the hospital.

On July 1, 1951, there was a 2 ounce hemoptysis, followed by blood streaked sputum for two weeks. The patient had continued to work.

The family history was negative for tuberculosis and tendencies to other known familial diseases. His mother and father had each lived to be 80 years of age. There had been no known exposure to tuberculosis.

The past history revealed that he had had measles and pertussis in infancy, diphtheria at six, and mumps and influenza at 20, all without known complications or sequelae. Until 16 years of age the general health had always been good. At that time, chronic gaseous dyspepsia appeared and persisted thereafter. There was never any nausea, vomiting, hematemesis, jaundice, melena or diarrhea. In 1922, after two attacks of appendicitis within one month, an appendectomy was performed; the appendix had ruptured. The wound drained for three weeks, then healed without known complications or sequelae. From 18 years of age to the present there were frequent sinus headaches, and from 30 years of age he had had frequent head, throat and chest colds. So far as he knew he had never had a nose, mouth, pharyngeal or laryngeal ulcer, otitis, cutaneous ulcer, enlargement of the lymph nodes, spleen or liver, or anemia. In 1939 he had passed a small urinary stone associated with severe pain for only two hours. He had always lived in northeastern New York State, in Clinton, Franklin or St. Lawrence counties, and he had been a farmer, timber

cutter, laborer or janitor. There had never been any unusual exposure to mineral, organic or other dusts, or to fowls, other birds or animals.

Physical examination on admission revealed a fairly well developed and nourished white male in no distress. The temperature was 99.4° F.; the pulse regular at 104 per minute; the respirations, 28; the blood pressure, 110 mm. Hg systolic and 80 mm. diastolic; the height, 5 feet 6 inches, and the weight, 133 pounds. He was edentulous. The tympanic membranes were slightly thickened and dull but not red or perforated. There was a small smooth tumor of the right true vocal cord over which the mucous membrane was intact; this tumor showed no change on comparison with the examination made four years previously. There were a moderate number of fine and medium rhonchi and a very few widely scattered moist râles over each lung. There was a well healed right lower quadrant abdominal operative scar, and bilateral moderate sized tense hydroceles. Negative findings of importance were: no fetor oris, cyanosis, local or general lymph node enlargement, cutaneous lesions, clubbing of the fingers, ulcers of the nose, mouth, pharynx or larynx, hepatomegaly, splenomegaly, or signs suggesting the presence of a malignant neoplasm. The chest roentgenogram (figure 1E) showed signs of numerous scattered areas of pulmonary disease throughout the upper half of each lung, most marked in the upper thirds, where there was evidence of a moderate sized cavity on each side. In the right hilar region there were a few irregular dense discrete shadows suggesting the presence of calcified or calcifying foci. The left costophrenic angle was blunt, and there were signs of partial calcification of the aortic arch. On comparison with the pre-admission film, taken approximately six weeks earlier, there had been slight clearing on the right and slight-to-moderate clearing on the left. It is to be emphasized here that he had continued to work until admission and had not received any treatment during this period.

The tuberculin test, using 0.1 mg. of O. T., and the histoplasmin test, using 0.1 c.c. of a 1:100 dilution, were each positive. A coccidioidin test using 0.1 c.c. of a 1:100 dilution was negative.

The sputum was negative for tubercle bacilli by concentration; negative for spores, yeast cells, mycelia and sulfur granules by direct microscopic examination; negative for fusospirochetal organisms by staining with gentian violet and Fontana's silver solution and by dark-field examination, but highly positive for elastic tissue. Cultures showed no significant pathogenic bacteria. Four weeks after inoculation, cultures for fungi were highly positive for *H. capsulatum*. The cultures at 37° C. on brain heart infusion agar with the addition of 10 per cent whole blood and 40 units of streptomycin and 20 units of penicillin per cubic centimeter of culture medium,^{22, 23} showed small moist dull brownish-white colonies (figure 2B) containing small oval budding cells in the yeastlike phase (figure 2C). The cultures at room temperature on Sabouraud's glucose agar showed large colonies with cottony white aerial mycelium (figure 2D). The organisms in this mycelial phase showed very delicate branching septate hyphae with the characteristic and diagnostic tuberculate chlamydospores or macroconidia²² (figure 2E). In thin smears of the sputum, prepared gently to prevent rupture of the cells and stained with Wright's stain, on prolonged search, using the oil immersion objective, intracellular parasites having the typical appearance of *H. capsulatum* were not seen.

No reactions were obtained in the complement fixation tests for histoplasmosis or blastomycosis, and significant agglutination was not obtained with *Brucella abortus* or *Bacterium tularensis*. The blood culture was negative for *H. capsulatum*. The red blood cell count was 5,060,000; the hemoglobin was 15.5 gm.; the hematocrit was 48; the white blood cell count was 14,200; the differential count showed neutrophils, 81; band forms, 6 per cent; lymphocytes 15; monocytes, 4; the erythrocyte sedimentation rate (Westergren) was 61 mm. in one hour; the serologic test for syphilis was

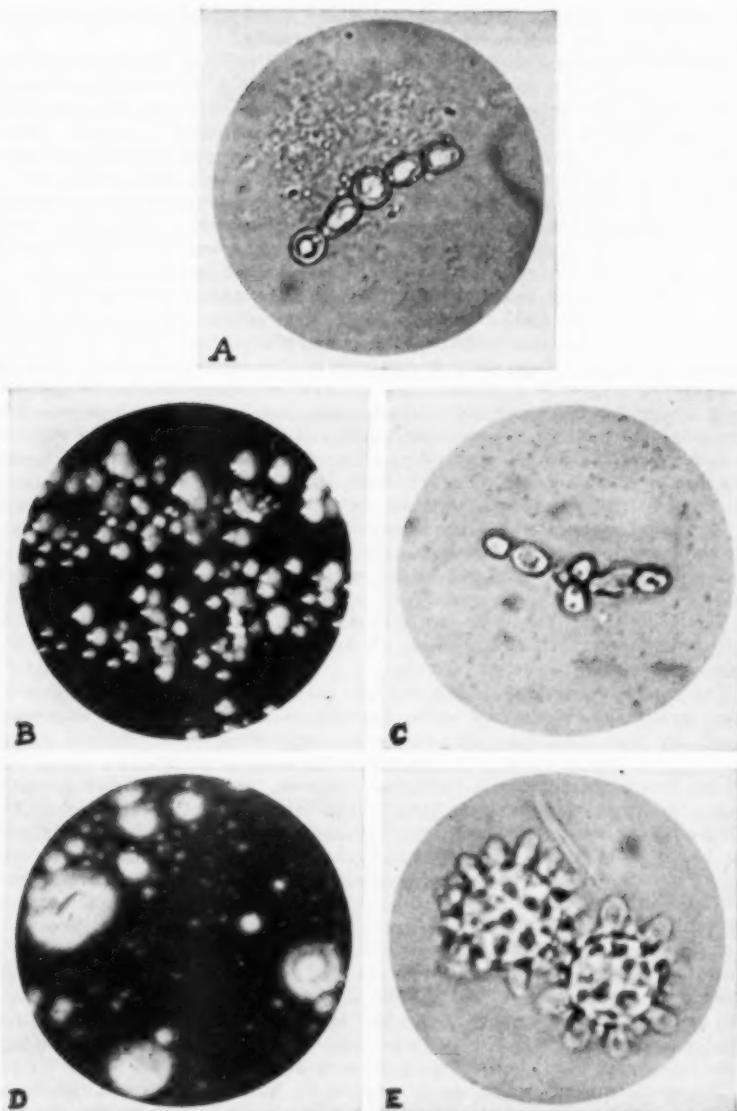


FIG. 2. *A*. Unstained wet preparation showing budding yeastlike cells from a fresh specimen of sputum cleared by adding a few drops of 10 per cent sodium hydroxide ($\times 1,000$). *B*. Pure culture of *H. capsulatum* isolated from a fresh specimen of sputum, after four weeks incubation at 37° C. on brain heart infusion agar with the addition of 10 per cent whole blood and 40 units of streptomycin and 20 units of penicillin per cubic centimeter of culture medium; the colonies are small, moist, dull brownish-white ($\times 5$). *C*. *H. capsulatum* cells in the yeastlike phase; taken from colonies in *B* ($\times 1,000$). *D*. Pure culture of *H. capsulatum* on

negative; the blood urea nitrogen was 7.7. On several occasions films of the peripheral blood, stained with Wright's stain, were studied at length, using the oil immersion objective, but intracellular parasites having the typical appearance of *H. capsulatum* were not seen.

The routine urinalysis gave normal findings. An electrocardiogram, including the 6 V and the 3 aV leads, was normal. A barium meal showed no abnormalities.

During the patient's course of seven weeks in the hospital he remained, in general, as on admission. During the first month there was low grade fever which only occasionally was as high as 99.6° F., and thereafter the temperature was normal. The cough decreased moderately, the average daily quantity of sputum fell to one-half ounce, and the character of the sputum remained unchanged except on August 12, 13 and 14, when there were moderately large hemoptyses followed by blood streaked sputum for several days. Because of the hemoptyses, bronchoscopy, which had been scheduled, was not performed.

Subsequent complete physical examinations showed no change except that during the early part of the second month of hospitalization painless otitis media with perforation of the tympanic membrane and slight purulent discharge developed on the right. A culture of this purulent discharge was negative for *H. capsulatum*. Numerous searches for cutaneous lesions and lymph nodes that could be biopsied were made, but none was found. There was never any ulcer of the nose, mouth, pharynx or larynx, and the spleen and liver were never palpable.

Five additional sputum specimens were reported negative for tubercle bacilli by concentration and culture. Six subsequent sputum specimens were each found highly positive for both elastic tissue and for *H. capsulatum* on culture. The sputum was repeatedly examined by direct smear and by culture for other pathogenic organisms, but none was found. However, after the diagnosis of histoplasmosis had been established by cultural methods, in unstained wet preparations of sputum cleared by adding a drop of 10 per cent sodium hydroxide, there were seen a very few small round, oval or pyriform, budding yeastlike cells, 2 to 4 μ in diameter, occurring singly, in short chains or small clusters.⁵³ These resembled the organisms in the yeastlike phase grown on cultures at 37° C. (figure 2A).

Two subsequent blood cultures were negative for *H. capsulatum*. Four additional blood specimens were examined, but no complement fixation reactions were obtained for histoplasmosis or blastomycosis, and significant agglutination was not obtained with *Br. abortus* or *Bact. tularensis*. Subsequent hemoglobin determinations were 16.5 and 17 gm. Three additional white blood cell counts were 18,800, 20,900 and 19,800. Subsequent differential counts showed no change except that on September 5, 1951, the eosinophil count was 14 per cent. Subsequent erythrocyte sedimentation rates were 60, 36 and 47. Six weekly urinalyses all gave normal findings except for microscopic hematuria on August 17, 1951.

Serial chest roentgenograms taken at biweekly intervals showed evidence of very slight improvement, but signs of bilateral cavitation in the upper thirds persisted (figure 1F). Roentgenograms of the abdomen in the anteroposterior and both oblique projections showed one very small dense discrete shadow on the right and two similar small dense discrete shadows on the left that remained within the outlines of the renal shadows on all films, and probably represented renal calculi. Also, there were signs of partial calcification of the prostate gland. Roentgenograms of the skull, paranasal sinuses, entire spine, pelvis and upper and lower extremities showed no abnormalities.

Sabouraud's glucose agar after 3 weeks incubation at room temperature; the colonies are large with cottony-white aerial mycelium (actual size). E. Characteristic or diagnostic tuberculate chlamydospores of *H. capsulatum*; taken from colonies as in D ($\times 1,000$).

A spirometric examination, for which the patient coöperated well, showed the following: The estimated normal vital capacity was 4,350 c.c.; the actual most-rapid-possible vital capacity was 4,250 c.c. in five seconds and 4,350 c.c. in 10 seconds; the resting minute ventilation was 13 L.; the maximum breathing capacity⁵² was 153 L. These findings are normal, and gave no evidence of lowered pulmonary ventilatory function.

The presence of a nontuberculous chronic cavitary pulmonary disease was indicated by failure to demonstrate tubercle bacilli in five specimens of sputum after concentration, or other pathogenic organisms by direct smear and culture, by repeated demonstration of elastic tissue, and by evidence in roentgenograms of bilateral moderately advanced pulmonary disease with a cavity in each apex. As the nature of the infection had not been demonstrated, a therapeutic test employing procaine penicillin, 300,000 units intramuscularly each 12 hours, and triple sulfonamides, 4 gm. initially, then 1 gm. each four hours day and night, was started on August 9 and continued through discharge one month later. As above noted, slight improvement followed, but more improvement had occurred before the antibiotic and drug therapy was instituted.

On September 9, seven weeks after admission, the patient left the hospital against medical advice because of nostalgia.

Following discharge he returned to his home, was up and about and did light chores. On reexaminations in the outpatient clinic made on September 22 and October 20, 1951, and on February 16, 1952, he appeared to be in a somewhat improved general condition and had gained 15 pounds in weight. There had been no fatigue, fever, chills or pain. The cough, expectoration and wheezing had persisted and, following each of several fresh colds, had temporarily increased. In addition, during the last week of September there was an hemoptysis of 1 ounce. Except for the gain in weight, complete physical examinations showed no change; signs of the disease in sites other than the lungs were not found, and there was no evidence that he had any other disease. On comparing serial chest roentgenograms, evidence of further slight clearing bilaterally was noted. Complete blood counts and routine urinalyses showed no change; the erythrocyte sedimentation rate fell to 21. Four subsequent complement fixation tests for evidence of histoplasmosis and blastomycosis showed negative reactions. The sputum continued to be odorless, mucopurulent, highly positive for elastic tissue, positive for *H. capsulatum* on culture, and negative for tubercle bacilli and other pathogenic organisms.

DISCUSSION

Diagnosis: The presumptive pre-admission diagnosis in this case was pulmonary tuberculosis. The clinical course had been consistent with this diagnosis, the tuberculin test was positive, and during the six weeks before admission the chest roentgenograms (figures 1D and E) had shown evidence of chronic bilateral upper lobe pulmonary disease of mixed bronchopneumonic and cavitary types. The patient had received no treatment, he was in fairly good general condition, had continued to work up to the day of admission, and was in no sense terminally or critically ill.

However, when numerous examinations of the sputum failed to reveal the presence of tubercle bacilli, and large amounts of elastic tissue were consistently found in the sputum, it was shown that the diagnosis of pulmonary tuberculosis was incorrect. Further studies were obviously needed.

The coccidioidin skin test was negative; the histoplasmin was positive *; no reactions were obtained in the complement fixation tests for histoplasmosis or blastomycosis, and significant agglutination was not obtained with *Br. abortus* or *Bact. tularensis*.† In addition, careful physical examinations showed no positive findings such as cutaneous lesions, enlarged lymph nodes or ulcerative or granulomatous lesions of the nose, mouth, pharynx or larynx that could be biopsied. More detailed microscopic examinations of the freshly collected odorless mucopurulent sputum revealed no sulfur granules, spores, yeast cells, mycelia or fusospirochetal organisms, and on culturing the sputum no significant pathogenic bacteria were found. The diagnosis of pulmonary histoplasmosis was established when cultures for fungi at both room and incubator temperature (37° C.) consistently showed numerous colonies of *H. capsulatum* (figures 2B, C, D, E) but no other fungi.

From the time of Darling's publications ^{1, 2, 3} until recently, histoplasmosis has been described as a chronic febrile illness in an emaciated patient having anemia, leukopenia, generalized lymph node enlargement, splenomegaly, hepatomegaly, and ulcerative or granulomatous lesions of the nose, mouth, pharynx or larynx. The patient whose case is being reported did have a chronic illness and occasional short periods of fever, but none of the other above mentioned classic findings was present. This lack suggests that, up to the present time at least, the disease is limited to the lungs. Since patients with histoplasmosis have not infrequently been found to have another disease also, careful search for such was made in this case but none was found.

The patient had a positive histoplasmin test, which has been considered evidence of a previous, or current, infection with *H. capsulatum*. Findings supporting this view have appeared in recently reported studies in which the specificity of the histoplasmin test was demonstrated in laboratory animals by performing skin tests both before and after experimentally produced infection with this fungus.^{35, 49} However, it is known ^{24, 51} that nonspecific reactions to histoplasmin are obtained at times in the presence of infection with *Blastomyces dermatitidis*, *Coccidioides immitis* and *Candida albicans*, and are apparently brought about by cross sensitivity with these fungi. Also, there is evidence that sensitivity to histoplasmin is depressed by critical illnesses, fever and old age, and that fluctuations in skin sensitivity occur during the illness even in proved cases.^{12, 17} These facts indicate that the lack of complete specificity of the histoplasmin skin test should be kept in mind.²⁴ Our patient had a negative coccidioidin test. In addition, the sputum, which was repeatedly and properly cultured for *B. dermatitidis* and *C. immitis*, was negative for these fungi.

On repeated examinations of the blood taken while the patient was hospitalized and following discharge, no positive reactions were obtained in the

* From Dr. Arden Howell, Jr., U. S. Public Health Service.

† Division of Laboratories and Research, New York State Department of Health.

complement fixation tests for histoplasmosis or blastomycosis. In a reported series of 10 proved cases of histoplasmosis with severe or progressive fatal clinical illness,¹⁸ in only one subject did the complement fixation test fail to demonstrate antibodies. However, it has been shown²⁵ that sera from chronic cases of histoplasmosis do not show titers that vary appreciably from those found in a small percentage of a normal population. Also, since the complement fixation titer has been reported high in acute cases of histoplasmosis, with a decrease in the titer as the disease becomes chronic, a transitory humoral response is thereby suggested. This may well be the explanation for the negative tests in our patient, who is undoubtedly in the chronic stage of the disease. In addition, there are cross reactions with other fungi.^{18, 26} Therefore, the reports of serologic studies should be interpreted with caution and in the light of the above facts.

Stained films of the peripheral blood were repeatedly searched for the presence of *H. capsulatum* and none was found. The lack of success by this most readily available and simplest method of diagnosis is not unusual,¹⁶ since this fungus is demonstrated in the circulating blood only intermittently, in very small numbers, or only during the terminal stages of the illness.²¹

In this case it is difficult or impossible to date accurately the onset of the present illness. Regarding this point, the portal of entry of the causative organisms into the body is of importance. The skin, the ears, the mouth, the lungs and the gastrointestinal tract have been mentioned as portals of entry. This patient had had, from the age of 16 years to the present, chronic gastrointestinal complaints which were severe enough to cause him to seek medical advice on numerous occasions. Even though examinations including a barium meal study were made, a diagnosis was never established. It is possible that the onset of the present illness occurred 40 years ago, at the time the gastrointestinal complaints appeared. DeMonbreun's experiments,²² in which he infected dogs by feeding them cultures of *H. capsulatum*, suggest that this fungus can survive exposure to gastric juice. Henderson et al.²² emphasized that their survey of the literature showed that ulcerative enteritis was frequently present in patients having histoplasmosis, even though conspicuous clinical evidence of such a condition had only rarely been mentioned. They concluded that, in almost every case, the gastrointestinal tract was probably the portal of entry of the organisms into the body, and that the spleen, liver, lungs and other structures were involved by lymphohematogenous metastasis. Raftery²³ reported that organisms morphologically identified as *H. capsulatum* were found in over 10 per cent of a group of 436 surgically removed appendices. Therefore, in order to date the onset of this patient's present illness, attempts were made to obtain the appendix which had been removed in 1922, but the surgical specimen had evidently been discarded.

When this patient was first examined in the outpatient clinic in 1939, 12 years before admission to the hospital, the presence of pulmonary disease on the right and bilateral pleural exudates were demonstrated by the chest

roentgenogram (figure 1A). It is our opinion that the present illness probably began at or shortly before this time. Subsequent chest roentgenographic examinations revealed that the signs of pulmonary disease and the right pleuritis had completely cleared by 1941 (figure 1C) and remained so through 1947. It has been shown^{13, 28} that a few patients with pulmonary disease from whose sputum or gastric contents *H. capsulatum* was isolated by culture have improved or recovered. In addition, that healing of histoplasmosis by fibrosis may occur is suggested by evidence obtained at some of the more recent necropsies in adults.²⁹ However, the onset of the present illness might well be dated as of March, 1951, only four months before admission, because it was at that time that severe and persistent complaints first appeared. Based on the fact that several patients with histoplasmosis had had otitis media, Humphrey³⁰ suggested that the ears could serve as the portal of entry of this fungus into the body. It is interesting to note that our patient had never had known ear disease, and that on admission physical examination of his ears showed no abnormality other than slight thickening of the tympanic membranes. However, during his hospital residence and while receiving penicillin and sulfonamide therapy, he developed painless purulent otitis media on the right with perforation of the tympanic membrane. Culture of this purulent discharge, which was scanty, was negative for *H. capsulatum*.

Various types of pulmonary lesions in patients with histoplasmosis have been described, such as interstitial pneumonitis, discrete or confluent areas of lobular pneumonia, miliary and larger nodules, granulomata, caseation necrosis, abscesses or cavities, fibrosis and calcifications.^{9, 16} The fact that there is no specific or uniform type of lung lesion is reflected by the lack of a characteristic pattern of abnormality shown on chest roentgenograms. Of the 65 cases with proved involvement of the lungs by histoplasmosis reported up to January 1, 1950, chest roentgenographic findings resembling the apical reinfection type of tuberculosis, as shown to be present in the case herein reported (figures 1D, E, F), were demonstrated in only four cases. In only three cases was evidence of pulmonary cavitation seen, and in these the cavities may not have been due to histoplasmosis, but proved cavitation has been demonstrated by examination of the surgical specimens in each of three reported cases which have been treated by pulmonary resection.^{21, 44} Pulmonary symptoms are likewise dependent on the location and the nature of the lung lesions. This patient had pleuritic pain associated with bilateral pleuritis with effusion (figure 1A), cough, expectoration of mucopurulent sputum, wheezing and repeated hemoptyses. Lesions produced by *H. capsulatum* have been frequently found in the subpleural tissues and in the pleura. Chest pain has been mentioned as a symptom of pulmonary histoplasmosis,^{28, 29, 44} pleural friction rubs were reported¹⁶ in several cases, and this fungus has been cultured from pleural fluid.²¹ Well stained organisms have been found in organizing inflammatory pleuritis, and fibrous adhesions or

fibrinopurulent pleural processes have frequently been noted.^{15, 20} Furthermore, and of interest here, it has been reported that three of five experimentally infected dogs developed bilateral pleural effusions in addition to pulmonary involvement.²⁶ Since this patient has been proved to have necrotic lung lesions, as shown by the presence of elastic tissue in the sputum, and bilateral abscesses or cavities, as demonstrated by chest roentgenograms (figures 1D, E, F), the causes for the cough, expectoration, wheezing and hemoptyses are obvious.

The findings described in this case demonstrate that the diagnosis of histoplasmosis can be established only by the demonstration of the fungus by laboratory methods. It must be emphasized that the great variability in the presenting symptoms and signs of this illness causes it to simulate many other diseases and thereby makes its clinical diagnosis very difficult or impossible. In this case, active bilateral apical cavitary and bronchopneumonic pulmonary tuberculosis was simulated.

Treatment: Numerous types of treatment, including iodides, arsenicals, mercurials, quinine, thymol, sulfonamides, Promin, actidione, penicillin, streptomycin, aureomycin, chloramphenicol, roentgen radiation and autogenous vaccines, have been used in treating patients with histoplasmosis and none has been satisfactory.^{16, 44, 31, 47} In a very few cases clinical improvement has followed the use of antimony or diamidine preparations.¹⁶ However, in three cases^{31, 45} stilbamidine, which has been shown to be effective against *H. capsulatum* *in vitro*,⁴⁶ was used without success. In each of these three cases there were lesions involving the skin or mucous membranes that could be followed by direct vision. Recently it has been reported⁴⁷ that ethyl vanillate, which has been shown to have fungicidal properties, was given to 12 patients with histoplasmosis, proved by culture, with the disseminated progressive type of the disease. Although the prognosis was poor for even weeks or months of life, five are alive and apparently well following treatment. However, the therapeutic range of this drug is narrow and the margin of safety undesirably small.

As described in the case report above, and as a planned therapeutic test started before the diagnosis was established, our patient was treated for one month with 300,000 units of procaine penicillin given intramuscularly each 12 hours and 1 gm. of triple sulfonamides given by mouth each four hours day and night. During this period of treatment no evidence of improvement was noted by comparing serial chest roentgenograms, and no more than very slight improvement occurred in the clinical manifestations of his disease. Of further interest is the fact that throughout this month of treatment the sputum remained positive by culture for *H. capsulatum*.

In 1951 Hodgson et al.²¹ described two cases of pulmonary histoplasmosis successfully treated by lobectomy. One patient was a 36 year old white man with a large cystic lesion in the right lower lobe; the other was a 34 year old white woman with scattered areas of disease in the right upper

lobe. When reported, these two patients had been followed postoperatively for two years and for six months, respectively, they were in good general condition and there was no sign of recurrence of the disease. Bettag⁴ reported a case very similar to the second case above mentioned. His patient, following a wedge resection of the disease in the right upper lobe, made an uneventful recovery and there has been no sign of recurrence during a follow-up period of one year.

Our patient, who was 56 years of age and in fairly good general condition, had a normal vital capacity and a normal maximum breathing capacity. Surgical treatment was considered but, because of his age and the extensive involvement throughout both upper lobes, it was decided that resection should not be attempted.

Prognosis: Regarding prognosis, Parsons and Zarafonetis¹⁶ in 1945, in keeping with information available at that time concerning 71 reviewed cases, stated that death had occurred a few weeks, months or rarely some years after the infection. In one small group of only four cases the course of the illness had varied from four to 16 years. Seabury³¹ in 1949 emphasized that histoplasmosis may remain a localized granuloma for a relatively long time. As information accumulates, the impression that recovery from this disease is possible is becoming more and more tenable, but there is no means of proving that the body is rid of the infection. Histoplasmosis may exist as a chronic illness for years and then an exacerbation may occur and prove fatal. Those more recent papers^{18, 17, 28, 32} concerning the benign forms of histoplasmosis, when considered along with previously held ideas, bring strongly into view the concept that the course of this disease and, by the same token, its prognosis are exceedingly variable and in these respects comparable to tuberculosis. The negative complement fixation tests in this case may furnish evidence that the disease is not severe or progressive¹⁸ and thereby point toward a good prognosis. Similarly Smith²⁶ showed that among patients with blastomycosis, the prognosis was best in those who had a positive skin test to either a vaccine or to blastomycin, but no antibodies in their sera demonstrable by complement fixation tests. Failure to demonstrate involvement in sites other than the lungs on repeated examinations suggests that this patient's disease is limited to the lungs and is not generalized.

Epidemiology: Until 1939, when DeMonbreun³³ reported an instance of histoplasmosis occurring spontaneously in a dog, *H. capsulatum* had not been found in nature other than in man. Recently, a survey³⁴ of the literature has shown that many dogs, domestic cats, house mice, brown rats, roof rats and, in addition, skunks and an opossum have been found to be naturally infected with this fungus. In one reported instance³⁶ an infected mouse and three infected dogs were found in the same household. Also, an epidemiologic study of histoplasmosis in cattle has been made,³⁵ and histoplasmin reactors were found. DeMonbreun³³ suggested that this disease might be

transmitted from the infected host by tick and insect bites. This possibility was later investigated³⁶ and *H. capsulatum* was recovered by culture from a tick after it had been allowed to feed on a heavily infected dog with a positive blood culture. Prior and Cole³⁷ reported that histoplasmosis developed in three of five dogs while they were exposed to eight dogs naturally infected with *H. capsulatum*; therefore, transmission of this infection from dog to dog has been shown. Contact between infected animals and human subjects having histoplasmosis has not been proved except by Para,³⁸ who reported a case in a child in Brazil who had had close association with a house dog from whose lung *H. capsulatum* was isolated. In 1946 McLeod et al.³¹ recorded that two brothers, aged six and eight years, had died of histoplasmosis, in each of whom the diagnosis was established ante mortem by cultures. This was the first reported instance of histoplasmosis in siblings. Wheeler et al.³² reported the occurrence in two cousins, aged five and one-half and eight years, who were constant companions, of simultaneous nonfatal systemic histoplasmosis, proved by blood culture. However, no report has been found of transmission of this infection from man to man, and at the present time the facts suggest that this disease is not transmitted in this manner.^{17, 39} This very important point has not been settled and, because of this lack of knowledge concerning the epidemiology of histoplasmosis, our patient has been instructed to exercise great care in personal hygiene and in the disposal of his highly positive sputum. To date, accumulated evidence indicates that in its mode of dissemination histoplasmosis resembles coccidioidomycosis⁴⁰ and not tuberculosis.⁴¹ Of great interest is the fact that Emmons^{42, 34} in Virginia and Grayson et al.⁴³ in Indiana have demonstrated that *H. capsulatum* can be isolated from the soil. Furthermore, it has been reported⁴² that the characteristic macroconidia, which have not been found in animal tissues, occur naturally in the soil. This observation indicates that this fungus has a saprophytic free-living existence in the soil. Furthermore, using experimental methods in the laboratory, *H. capsulatum* has been shown to grow, sporulate and produce macroconidia in previously sterilized soil. These facts may prove to be of significance concerning the epidemiology of histoplasmosis in both man and animals. DeMonbreun⁴ reported that the yeastlike forms of this fungus are so resistant to drying that after being removed from cultures and kept at room temperature many remain viable for two months or more, and that they withstand a temperature of 45° C. for 30 minutes but are killed when exposed to 55° C. for 30 minutes. Upon studying the mycelial form, this same investigator found that some of the ascus-like cells will germinate following an exposure of 30 minutes to 55° C., but no viable forms were found in dextrose agar cultures kept at room temperature for four months or longer. On the other hand, and of much importance from the standpoint of both epidemiology and diagnosis, Kurung³³ has recently shown that *H. capsulatum* can be cultured from sputum only if the specimen is no older than 48 hours.

This latter observation lends evidence that the organisms in expectorated sputum remain infectious for only a relatively short period.

The individual whose case is herein reported had never had any known contact with ill animals. He had been a farmer, timber cutter, laborer or janitor and had always been a resident of northeastern New York State and had never traveled outside of the State.

SUMMARY

A case is reported of chronic bilateral upper lobe pulmonary histoplasmosis of mixed bronchopneumonic and cavitary types in a 56 year old white man from whose sputum *Histoplasma capsulatum* has been repeatedly isolated by culture. Signs of the disease in sites other than the lungs, and evidence of any other disease, have not been detected.

This is the first case of proved histoplasmosis ever reported in a life-long resident of New York State⁴⁶ who has never traveled outside of the State.

BIBLIOGRAPHY

1. Darling, S. T.: A protozoan general infection producing pseudotubercles in the lungs and focal necroses in the liver, spleen and lymph nodes, J. A. M. A. **46**: 1283, 1906.
2. Darling, S. T.: Histoplasmosis: a fatal infectious disease resembling kala-azar found among natives of tropical America, Arch. Int. Med. **2**: 107, 1908.
3. Darling, S. T.: The morphology of the parasite (*Histoplasma capsulatum*) and the lesions of histoplasmosis, a fatal disease of tropical America, J. Exper. Med. **11**: 515, 1909.
4. Riley, W. A., and Watson, C. J.: Histoplasmosis of Darling: case originating in Minnesota, Am. J. Trop. Med. **6**: 271, 1926.
5. Phelps, B. M., and Mallory, F. B.: Fifteenth Ann. Rep. Med. Dept. United Fruit Co. pp. 115-122, 1926.
6. DeMonbreun, W. A.: The cultivation and cultural characteristics of Darling's *Histoplasma capsulatum*, Am. J. Trop. Med. **14**: 93, 1934.
7. Dodd, K., and Tompkins, E. H.: A case of histoplasmosis of Darling in an infant, Am. J. Trop. Med. **14**: 127, 1934.
8. Conant, N. F.: A cultural study of the life cycle of *Histoplasma capsulatum* Darling, 1906, J. Bact. **41**: 563, 1941.
9. Tager, M., and Liebow, A. A.: Observations on histoplasmosis, Yale J. Biol. and Med. **14**: 469, 1942.
10. Christie, A., and Peterson, J. C.: Pulmonary calcification in negative reactors to tuberculin, Am. J. Pub. Health **35**: 1131, 1945.
11. Palmer, C. E.: Non-tuberculous pulmonary calcification and sensitivity to histoplasmin, Pub. Health Rep. **60**: 513, 1945.
12. White, F. C., and Hill, H. E.: Disseminated pulmonary calcification, Am. Rev. Tuberc. **62**: 1, 1950.
13. Bunnell, I. L., and Furcolow, M. L.: A report on ten proved cases of histoplasmosis, Pub. Health Rep. **63**: 299, 1948.
14. Curtis, A. C., and Grekin, J. N.: Histoplasmosis. A review of the cutaneous and adjacent mucous membrane manifestations with a report of three cases, J. A. M. A. **134**: 1217, 1947.
15. Meleney, H. E.: Histoplasmosis, a review, Am. J. Trop. Med. **20**: 603, 1940.

16. Parsons, R. J., and Zarafonetis, C. J. D.: Histoplasmosis in man, Arch. Int. Med. **75**: 1, 1945.
17. Beadenkopf, W. G., and Loosli, C. G.: Histoplasmosis, tuberculosis and coccidioidomycosis, J. A. M. A. **146**: 621, 1951.
18. Furcolow, M. L., Mantz, H. L., and Lewis, I.: The roentgenographic appearance of persistent pulmonary infiltrates associated with sensitivity to histoplasmin, Pub. Health Rep. **62**: 1711, 1947.
19. Palmer, C. E.: Geographic differences in sensitivity to histoplasmin among student nurses, Pub. Health Rep. **61**: 475, 1946.
20. Meleney, H. E.: Pulmonary histoplasmosis, Am. Rev. Tuberc. **44**: 240, 1941.
21. Hodgson, C. H., Weed, L. A., and Clagett, O. T.: Pulmonary histoplasmosis, J. A. M. A. **145**: 807, 1951.
22. Thompson, L.: Note on a selective medium for fungi, Proc. Staff Meet., Mayo Clin. **20**: 248, 1945.
23. Campbell, C. C., and Saslaw, S.: Enhancement of growth of certain fungi by streptomycin, Proc. Soc. Exper. Biol. and Med. **70**: 562, 1949.
24. Emmons, C. W., Olson, B. J., and Eldridge, W. W.: Studies of the role of fungi in pulmonary disease, Pub. Health Rep. **60**: 1383, 1945.
25. Campbell, C. C., and Saslaw, S.: Use of yeast-phase antigens in a complement fixation test for histoplasmosis, Pub. Health Rep. **64**: 551, 1949.
26. Smith, D. T.: Immunologic types of blastomycosis, Ann. Int. Med. **31**: 463, 1949.
27. Henderson, R. G., Pinkerton, H., and Moore, L. T.: *Histoplasma capsulatum* as a cause of chronic ulcerative enteritis, J. A. M. A. **118**: 885, 1942.
28. Johnson, H. E., and Batson, R.: Benign pulmonary histoplasmosis, Dis. of Chest **14**: 517, 1948.
29. Conant, N. F., Martin, D. S., Smith, D. T., Baker, R. D., and Callaway, J. L.: Manual of clinical mycology, 1944, W. B. Saunders Company, Philadelphia, pp. 151-165.
30. Humphrey, A. A.: Reticul endothelial cytomycosis, Arch. Int. Med. **65**: 902, 1940.
31. Seabury, J. H.: Stilbamidine in the treatment of histoplasmosis: two case reports, Ann. Int. Med. **31**: 520, 1949.
32. Wheeler, W. E., Friedman, V., and Saslaw, S.: Simultaneous nonfatal systemic histoplasmosis in two cousins, Am. J. Dis. Child. **79**: 806, 1950.
33. DeMonbreun, W. A.: The dog as a natural host of *Histoplasma capsulatum*: case of histoplasmosis in this animal, Am. J. Trop. Med. **19**: 565, 1939.
34. Emmons, C. W.: Histoplasmosis: animal reservoirs and other sources in nature of the pathogenic fungus, histoplasma, Am. J. Pub. Health **40**: 436, 1950.
35. Ruhe, J. S., and Cazier, P. D.: A review of histoplasmosis, J. Am. Vet. M. A. **115**: 47, 1949.
36. Olson, B. J., Bell, J. A., and Emmons, C. W.: Studies on histoplasmosis in a rural community, Am. J. Pub. Health **37**: 441, 1947.
37. Prior, J. A., and Cole, C. R.: Studies on the communicability of histoplasmosis, Am. Rev. Tuberc. **63**: 538, 1951.
38. Para, M.: Histoplasmosis in Brazil, Am. J. Trop. Med. **26**: 273, 1946.
39. Ferebee, S. H., and Furcolow, M. L.: Histoplasmin sensitivity among siblings, Pub. Health Rep. **62**: 834, 1947.
40. Smith, C. E.: Coccidioidomycosis, M. Clin. North America **27**: 790, 1943.
41. Opie, E. L., and McPhedran, F. M.: The contagion of tuberculosis, Am. Rev. Tuberc. **14**: 347, 1926.
42. Emmons, C. W.: Isolation of *Histoplasma capsulatum* from soil, Pub. Health Rep. **64**: 892, 1949.
43. Grayson, J. T., Loosli, C. G., and Alexander, E. R.: The isolation of *Histoplasma capsulatum* from soil in an unused silo, Science **114**: 323, 1951.
44. Bettag, O. L.: Pulmonary resection for histoplasmosis, J. Thoracic Surg. **22**: 434, 1951.

45. Burden, J. F.: Personal communication.
46. Seabury, J. H., and Artis, D.: In vitro susceptibility of *Histoplasma capsulatum* to therapeutic agents, Proc. Soc. Exper. Biol. and Med. **61**: 15, 1946.
47. Christie, A., Middleton, J. G., Peterson, J. C., and McVickar, D. L.: Treatment of disseminated histoplasmosis with ethyl vanillate, Pediatrics **7**: 7, 1951.
48. Raftery, A.: Subclinical histoplasmosis, J. A. M. A. **145**: 216, 1951.
49. Scheff, G. J., and Pfeifer-Scheff, I. M.: The cellular and immunological reactions in rabbits infected with *H. capsulatum*, Am. Rev. Tuberc. **62**: 374, 1950.
50. Ziegler, E. E.: Histoplasmosis of Darling: review and case report with autopsy, Ann. Int. Med. **24**: 1073, 1946.
51. McLeod, J. H., Emmons, C. W., Ross, S., and Burke, F. G.: Histoplasmosis—a report of four cases, two in siblings. Histoplasmin test and other diagnostic procedures, J. Pediat. **28**: 275, 1946.
52. Cournand, A., Richards, D. W., Jr., and Darling, R. C.: Graphic tracings of respiration in study of pulmonary disease, Am. Rev. Tuberc. **40**: 487, 1939.
53. Kurung, J. M.: The isolation of *Histoplasma capsulatum* from sputum, Am. Rev. Tuberc. **66**: 578, 1952.

FAILURE OF SURGERY TO RELIEVE SYMPTOMS IN PROLAPSE OF THE GASTRIC MUCOSA THROUGH THE PYLORUS *

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THE current literature is replete with reports of prolapse of the gastric mucosa through the pylorus as a prominent cause of symptoms.^{1, 2, 3, 4, 5} The latter have usually been described as nonspecific, and include epigastric pain, burning and fullness, nausea, vomiting and even hemorrhage. While the etiology of the condition is unknown, it is generally believed to be due to an increase in the normal mobility of the antral mucosa over the muscularis, with propulsion of the redundant mucosa through the pylorus during peristalsis. Thus the symptoms have been ascribed to a localized gastritis of the extruded mucosa, or to an intermittent obstruction of the pylorus produced by the prolapsing mucosa, with hemorrhage resulting from erosions caused by the constricting action of the pyloric ring.

The diagnosis is made primarily by x-ray with the demonstration of a mushroom- or cauliflower-shaped defect of the base of the duodenal bulb. Since the phenomenon of prolapse is a fleeting one, the x-ray finding is usually transient and may escape detection or be noted on only a single of many films taken of the pyloroduodenal region. Obstruction of the pyloric lumen by the prolapsing folds resulting in gastric retention has rarely been demonstrated radiologically.

Nearly all authors have emphasized the relative rarity of this condition and its importance as a clinical entity due to its variable symptoms, its elusiveness on x-ray and the liability to occult or massive hemorrhage. Scott¹ believes that transpyloric mucosal prolapse is always clinically significant, since he failed to observe a single instance in 200 patients who were free of gastrointestinal symptoms.

Although most cases have been treated conservatively, surgery has been recommended for patients whose symptoms persist despite a bland diet and antispasmodics. Kaplan and Shepard⁶ state that failure to respond to a medical régime after one month is an indication for surgery. They recommend pyloroplasty with excision of the redundant antral mucosa.

Contrary to the above observations, Rappaport, Rappaport and Stanton⁷ recently reported that prolapse of the gastric mucosa through the pylorus is a relatively common radiologic finding, occurring in normals as well as in patients with symptoms and pathology unrelated to the stomach. In a subsequent communication we⁸ reported the presence of prolapsing gastric

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mucosa in 155 (15.5 per cent) of 1,000 consecutive patients. It was found in the absence of digestive complaints and in conjunction with all the common diseases of the gastrointestinal tract. Furthermore, the characteristic symptoms of the latter were unaltered by the concomitant transpyloric mucosal prolapse. It was our opinion that this radiologic phenomenon is not pathologic and is rarely a primary cause of symptoms. Mucosal extrusion was considered due to gastric hyperperistalsis, motivated either by a local disease such as peptic ulcer, or by neurogenic factors in the absence of organic disease. Thus when symptoms are present they are usually due to the primary disorder, the prolapse *per se* playing an insignificant clinical rôle. Corroboratory views relative to its incidence and clinical significance were presented by Levin and Felson⁸ and by Bartels and Eltorm.¹⁰

It is our purpose to report four cases of prolapse of the gastric mucosa into the duodenum who were subjected to surgery and who subsequently developed recurrence of their symptoms.

CASE REPORTS

Case 1. A 57 year old male had noted recurrent epigastric discomfort and nausea shortly after meals for many years. He had always been high-strung, with a tendency to depressed moods, and found his epigastric symptoms coincided with periods of emo-

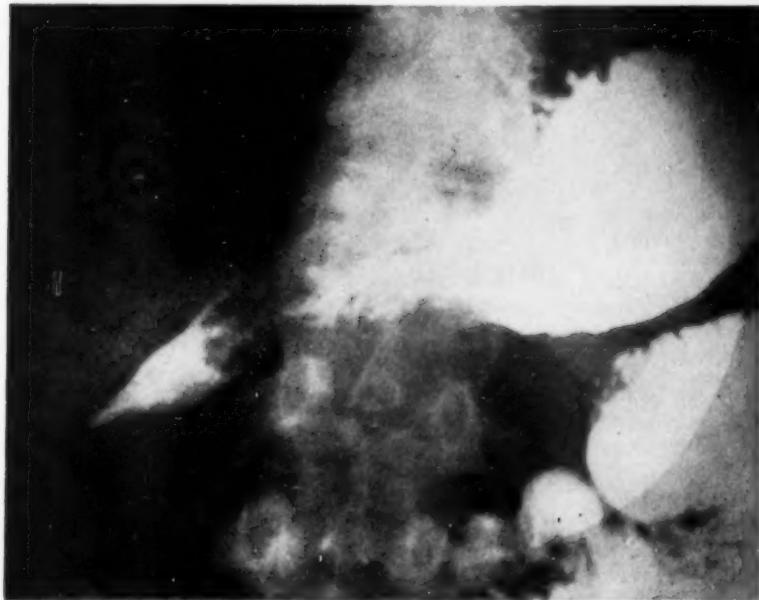


FIG. 1a. (*Case 1*) Preoperative x-ray demonstrating prolapse of the antral mucosa into the base of the duodenal bulb. At operation the degree of prolapse was considerably greater than that observed radiologically.



FIG. 1b. (Case 1) Section through the stomach showing hypertrophy of the pylorus (A) and prolapsed gastric mucosa (B) lying on the duodenal side of the pylorus. A mild gastritis was found.

tional tension. He did not drink or smoke. In 1938 he was hospitalized because of paroxysmal tachycardia. In 1939 a gastrointestinal series was done because of his recurrent dyspepsia, and he was told there was a questionable duodenal ulcer. An ulcer régime, however, failed to relieve his symptoms. In August, 1949, upon arriving in Atlantic City on vacation, he developed severe nausea, epigastric burning and vomiting, and was admitted to the Atlantic City Hospital. After several days he was transferred to Mary Immaculate Hospital. X-rays revealed a hiatus hernia and prolapse of the gastric mucosa through the pylorus. He was treated with intravenous fluids until the nausea and retching ceased and was discharged after one week. During the subsequent year he experienced frequent recurrences of postprandial nausea and epigastric fullness, unrelieved by sedation, antispasmodics or aluminum gels. There was no relationship between his symptoms and the recumbent position. Again in August, 1950, within a few hours of reaching Atlantic City for a holiday, he developed an acute exacerbation of these symptoms and on August 13 was admitted to Mary Immaculate Hospital with nausea and vomiting. He complained that his "stomach felt blocked." X-rays again demonstrated a reducible hiatus hernia and prolapse of the antral mucosa (figure 1a). There was no evidence of pyloric obstruction, and the stomach emptied rapidly. Gallbladder series was normal. On August 20 he was examined by the senior author, who concluded that this was a case of cyclic vomiting due to gastric neurosis, and that neither the hiatus hernia nor the prolapsing gastric mucosa was the primary cause of his recurrent symptoms. He was treated with parenteral fluids and his nausea and vomiting gradually ceased.

He was re-admitted to the same hospital October 1, 1950, with a mild recurrence of the above complaints, and on October 5 a subtotal gastric resection was performed. The surgeon reported that in the antrum a soft mass could be felt consisting of gastric mucosa which could be folded up and pushed through the pylorus. The pylorus felt thickened.

One week following the operation the patient complained that his stomach felt "blocked," and nausea, retching and vomiting recurred. Parenteral feeding was again started and he was finally discharged after three weeks, with little improvement. He was re-admitted to the hospital with the same complaints two weeks later. Despite his continued nausea and retching there was no abdominal pain or tenderness; his temperature and pulse remained normal, and the gastroenterostomy stoma showed no obstruction. Psychotherapy was suggested but the patient refused this approach. His symptoms gradually subsided and he was discharged from the hospital. Several months later, shortly after his arrival at Atlantic City on vacation, he again experienced an acute recurrence of nausea and vomiting, unattended by abdominal pain. These symptoms gradually subsided without necessitating hospitalization.

Pathologic Findings: The mucosa in the antrum and pyloric region was quite loose and freely movable and could be readily prolapsed 2 cm. into the duodenum. There was moderate hypertrophy of the pylorus, especially in the posterior aspect (figure 1b). No ulcerations were seen. On microscopic examination the mucosa was composed of uniform glands, interspersed among them a few inflammatory cells. There was an increase in thickness and hyperplasia of the pyloric muscularis.

Diagnosis: (1) Hypertrophy of the pylorus. (2) Prolapse of the gastric mucosa through the pylorus. (3) Mild gastritis.

Case 2. A 41 year old male jeweler had a 10 year history of recurrent epigastric burning radiating to the precordium, nausea and persistent belching. These symptoms would start shortly after eating, particularly if the meal was heavy or included spicy foods. Relief was obtained by soda or any medication which caused belching. He felt better if he omitted a meal, and on occasion would induce vomiting for relief. He noted his symptoms came on during periods of emotional tension, but while on vacation he usually felt well and could eat all foods with impunity. He had been in

the Army for one year, and was x-rayed on several occasions because of his continuous dyspepsia. A questionable duodenal ulcer had been found on one occasion, but he never obtained relief from an ulcer régime. Milk exacerbated his symptoms, causing increased bloating and diarrhea. Despite his chronic gastric complaints there had been no weight loss, and he had always been considerably overweight. In January, 1948, his wife was hospitalized with a threatened abortion and within 24 hours he developed severe nausea, retching and persistent epigastric burning, unrelieved by any medication. He was hospitalized and fed parenterally for four days. A gastrointestinal series was reported as showing large gastric rugae suggesting hypertrophic gastritis with prolapse of the antral mucosa into the duodenum. Surgery was recom-



FIG. 2. (Case 2) Characteristic umbrella-shaped defect at the base of the duodenal bulb produced by prolapsing gastric mucosa. Although the antral folds appear hypertrophic, there was no evidence of gastritis at gastroscopy or in the resected specimen.

mended but the patient declined and, following discharge, was referred for evaluation.

Physical examination was not remarkable apart from obesity (210 pounds). Gallbladder, barium enema, sigmoidoscopy, blood count, gastric analysis, electrocardiogram and stool survey for blood, ova and parasites were normal. X-rays revealed a normal stomach, with intermittent prolapse of the gastric mucosa through the pylorus of moderate degree. The duodenal bulb was normal and the stomach emptied rapidly. The small intestinal pattern was normal. Gastroscopy failed to disclose evidence of gastritis. The antral folds did not appear hypertrophic.

In the absence of organic findings the patient was placed on a bland, low residue diet excluding milk and milk products. Small meals were prescribed and he was ad-

vised to lose weight. Trasentine and phenobarbital were given before meals and he was warned against eating rapidly or when he was under severe emotional tension. On this régime he lost 30 pounds and remained asymptomatic for 14 months. He was x-rayed on March 14, 1949, and again the stomach appeared normal, with no change in the transpyloric mucosal prolapse (figure 2).

He moved to the Midwest where, following business reverses, he developed recurrence of his original symptoms. He was hospitalized there in January, 1950, and a subtotal gastric resection was done for prolapse of the gastric mucosa. He felt well for five months following surgery but in July 1950 he noted a gradual recurrence of epigastric burning, fullness and nausea which became progressively worse, and he was rehospitalized. X-ray findings were normal. He was given Banthine without benefit. Because of continued symptoms he returned here for evaluation June 12, 1951.

Physical findings were not remarkable. X-rays revealed a normal gastric stump and stoma. The small intestinal pattern was normal. Gastric analysis showed a low free acid, and gastroscopy was normal. Blood count, glucose tolerance and liver function studies were normal.

It was our impression that his symptoms were functional. He was again placed on small bland feedings with Donnatal before meals and noted gradual improvement. When seen again, in February, 1952, he reported only occasional epigastric fullness when under emotional stress.

Operative Findings: In the prepyloric region a small soft mass was palpable which could be pushed into the duodenum. Resection of two thirds of the stomach and 2 cm. of the duodenum was performed. On opening the specimen the mass consisted of redundant antral mucosa. The duodenum was normal.

Pathologic Findings: Normal gastric mucosa; normal duodenum.

Case 3. A 38 year old male commercial artist had been subject for 12 years to frequent epigastric cramping pain, heartburn and nausea, coming on shortly after eating. He noted some relief with antacids and when on a bland diet. He was a rapid eater and a heavy smoker. Belching was marked throughout the day and gave transient relief. He related his symptoms primarily to emotional tension associated with his occupation. He had been x-rayed on several occasions with negative findings, but on one occasion, in the Army, was told there was a possible polyp in the antrum. In January, 1948, a diagnosis of prolapse of the gastric mucosa into the duodenum was established by x-ray, and a pyloroplasty with resection of the redundant antral folds was done.

He felt well for four months after the operation, during which time he maintained a bland diet and curtailed his work. When he resumed his usual habits, however, his original symptoms gradually recurred, associated with occasional retching. He was referred for evaluation February 14, 1949.

Physical findings were not remarkable. Marked aerophagia was noted. X-rays showed a normal stomach. The pyloroduodenal region was examined through many peristaltic cycles and no prolapsing antral mucosa was found. The stomach emptied rapidly and the duodenal bulb was normal. Gallbladder series was normal. Gastric analysis, blood count and stools were normal. Gastroscopy revealed no mucosal abnormalities.

It was our opinion that this patient's symptoms were due to faulty eating habits and emotional tension. Six months later, because of many functional symptoms referable to other systems, he was referred for psychotherapy. After eight months there was considerable improvement. He has remained relatively well under the care of a psychiatrist.

Operative Findings: The stomach was opened in its long axis near the pylorus. There was redundant antral mucosa which could be readily pushed into the duodenum.

No ulcer or polyp was seen. The redundant mucosa was excised, the gastrotomy opening closed and a Finney pyloroplasty done.

Pathologic Report: Normal gastric mucosa.

Case 4. A 34 year old salesman was referred in July, 1947, with a six year history of intermittent epigastric pain, nausea, bloating and occasional vomiting following spicy foods. He felt fairly well if he observed a bland diet. The epigastric pain



FIG. 3. (*Case 4*) Massive prolapse of antral mucosa into the duodenum, with a coarse mucosal pattern of the entire stomach due to severe hypertrophic gastritis. Epigastric pain and hemorrhage recurred following subtotal gastric resection.

was not relieved by milk and only slightly by antacids. There were long periods of remission from symptoms, and he had noted no weight loss. On one occasion he observed tarry stools for a 24 hour period.

Examination revealed slight epigastric tenderness but was otherwise normal. X-rays showed a marked generalized hypertrophy of the gastric mucosa, with intermittent prolapse of the antral mucosa through the pylorus of massive degree (figure

3). The stomach emptied rapidly and the remainder of the gastrointestinal tract was normal. Blood count, gastric analysis and stools were normal. Gastroscopy confirmed the presence of a giant benign gastritis involving the entire stomach, with large folds which appeared to be extruded through the pylorus when peristalsis passed through the antrum. Two polyps were seen on the anterior wall below the cardia, both appearing benign.

Because of the extensive gastric involvement it was our opinion that only a total gastrectomy would prove curative. In view of his ability to remain relatively symptom-free on a bland diet, a conservative course was recommended. He remained well until January, 1948, when, following an upper respiratory infection, he noted recurrence of postprandial epigastric burning, nausea, anorexia and finally melena. He was hospitalized and a subtotal resection was done. The surgeon reported that a soft mass was felt in the antrum which could be pushed back and forth through the pylorus. The resected specimen revealed a severe hypertrophic gastritis, with marked prolapse of the antral rugae through the pylorus. No localized source of bleeding was found, nor were any polyps found in the resected stomach. Postoperative x-rays indicated that less than half of the stomach had been resected and that the rugal pattern was extremely coarse.

He felt fairly well for seven months but then experienced gradual recurrence of epigastric fullness, burning and nausea. In May, 1951, he was hospitalized because of hematemesis and melena. Profuse bleeding continued for 24 hours, necessitating 3,000 c.c. transfusions. Laparotomy was performed and nearly the whole of the remaining stomach was resected. The specimen showed a severe generalized hypertrophic gastritis with three benign polyps. An ulcer on the surface of one polyp was the site of hemorrhage. The patient made an uneventful recovery and has remained well for eight months except for his inability to regain his normal weight.

DISCUSSION

In view of numerous reports citing the importance of prolapse of the gastric mucosa through the pylorus as a cause of chronic gastric symptoms and the favorable results of surgery, an increase in the latter method of treatment is to be anticipated. Kaplan and Shepard⁶ reviewed the results of surgery in 44 cases and concluded that pyloroplasty with excision of the extruded antral mucosa was the best method of treatment for patients who did not benefit from a medical régime. However, in 22 of the above cases the favorable report was based upon a postoperative follow-up period of three months or less. Of the remaining 22 patients, five developed recurrence of symptoms and another required subsequent surgery because of pyloric obstruction, while three others died between one week and four months after operation.

Although hemorrhage has been reported as a common complication of prolapsing gastric mucosa, a definitive site of bleeding has rarely been established in cases subjected to surgery. Thus 13 of the 44 cases above cited were operated on because of hematemesis or melena, yet authentication of the antral mucosa as the site of bleeding was obtained in only two. Again the follow-up period in patients operated on for gross hemorrhage was too brief to evaluate the benefits of surgery, but in this group two suffered subsequent hemorrhage, one developed recurrence of symptoms, another died four months after operation, and one required secondary surgery.

We have presented four cases who were operated on because of symptoms attributed to prolapsing gastric mucosa, and whose symptoms recurred despite the elimination of the herniated mucosa either by gastric resection or by local excision. Since three patients experienced relief for periods ranging from four to seven months following surgery, had the results been assessed on the basis of only a three month follow-up period a most favorable impression would have been attained. However, all had even longer periods of spontaneous remissions prior to operation. The poor surgical results can be attributed directly to the fact that the symptoms were unrelated to the extrusion of gastric mucosa into the duodenum. Thus the complaints in cases 1, 2 and 3 were primarily psychosomatic and, despite the presence of prolapse of considerable degree in each case, pathologic changes in the involved mucosa were insignificant. It is noteworthy that in case 1, despite the complaint of a "blocked stomach" and the presence of moderate hypertrophy of the pylorus, there was no x-ray evidence of pyloric obstruction and the same sensation persisted after subtotal gastric resection. The acute recurrence of symptoms on three occasions upon arriving in Atlantic City suggests a conditioned psychic stimulus. In case 4, with a severe hypertrophic gastritis and an episode of hemorrhage prior to operation, the recurrence of both the dyspepsia and bleeding indicates that removal of prolapsed mucosa alone is ineffectual in the treatment of pathologic changes that involve other portions of the stomach.

Our studies indicate that transpyloric mucosal prolapse is a common radiologic finding which is rarely a primary cause of symptoms. Hence all other causes for gastric complaints, both organic and functional, must be considered before subjecting the patient to surgery for this condition. Finally, in the event of repeated upper gastrointestinal hemorrhage requiring surgical intervention, where no abnormality other than prolapsing gastric mucosa is found on x-ray and the cause of previous hemorrhage cannot be determined even at operation, a high subtotal gastric resection should be done rather than mere excision of the redundant antral mucosa. The more drastic procedure will at least safeguard against further hemorrhage from a peptic ulcer, which is commonly associated with prolapsing gastric mucosa and which cannot always be detected by the surgeon at operation.

BIBLIOGRAPHY

1. Scott, W. G.: Radiographic diagnosis of prolapsed redundant mucosa into the duodenum, with remarks on the clinical significance and treatment, *Radiology* **46**: 547, 1946.
2. Bralow, S. P., and Melamed, M.: Prolapse of redundant or hypertrophied gastric mucosa, *Am. J. Digest. Dis.* **14**: 215, 1947.
3. Manning, I. H., and Highsmith, G. P.: Prolapse of the gastric mucosa through the pylorus into the duodenum, *Gastroenterology* **10**: 643, 1948.
4. Wilson, F. W., and Granger, W. H.: Clinical aspects of prolapsed gastric mucosa, *Am. J. Digest. Dis.* **16**: 129, 1949.
5. Melamed, A.: Etiology and pathogenesis of prolapsed gastric mucosa into the duodenum, *Am. J. Digest. Dis.* **17**: 4, 1950.

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6. Kaplan, I. W., and Shepard, R. M.: Prolapse of the gastric mucosa into the duodenum, *J. A. M. A.* **147**: 554, 1951.
7. Rappaport, E. M., Rappaport, E. O., and Stanton, A.: Prolapse of the gastric mucosa through the pylorus with concomitant gastrointestinal pathology, *Rev. Gastroenterol.* **18**: 473, 1951.
8. Rappaport, E. M., Rappaport, E. O., and Alper, A.: Incidence and clinical significance of prolapse of the gastric mucosa through the pylorus, *J. A. M. A.* **150**: 183, 1952.
9. Levin, E. J., and Felson, B.: Asymptomatic gastric mucosal prolapse, *Radiology* **57**: 514, 1951.
10. Bartels, E. D., and Eltorm, H.: Prolapse of the gastric mucosa through the pylorus; physiological or abnormal? *Gastroenterology* **20**: 100, 1952.

FAILURE OF CORTISONE AND ACTH IN TREATMENT OF THE MORPHINE ABSTINENCE SYNDROME *

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RECENTLY considerable interest has been expressed in the possible ameliorating effects of cortisone and adrenocorticotropic hormone of the anterior pituitary on the symptoms of withdrawal of morphine and related drugs from addicted persons. Rowe¹ and co-workers have reported that ACTH and cortisone relieved symptoms of abstinence from meperidine (Demerol). Boswell² reported beneficial results with cortisone in combined addiction to meperidine and morphine. Hogness³ found that intravenous infusions of ACTH reduced or abolished withdrawal symptoms in 12 of 19 patients presumed to be addicted to heroin. On the other hand, Thorn⁴ and co-workers attempted to withdraw narcotics in one case of codeine addiction and one case of morphine addiction during ACTH therapy without success.

In view of these conflicting reports and in view of the difficult problems in establishing proper controls in studying narcotic addiction outside of special institutions, experiments designed to test the efficacy of cortisone and ACTH in alleviating symptoms of abstinence from morphine were carried out under closely controlled conditions.

METHOD OF INVESTIGATION

General Plan: The subjects, who volunteered for the experiments, were white male patients addicted to large amounts of heroin or morphine. Only patients who exhibited moderate to severe symptoms of abstinence in the first 48 hours following admission to the Public Health Service Hospital, Lexington, Kentucky, were selected for study. After patients were chosen they were transferred to a special ward devoted to clinical investigations of drug addiction. Patients were under constant 24 hour observation by specially trained attendants, and extreme precautions were taken to prevent the introduction of drugs, other than those prescribed, into the environment. In the research ward, morphine sulfate was administered subcutaneously four times daily, and the dose was increased or decreased until a dosage level was ascertained which would just prevent the appearance of withdrawal signs in each subject. This dose was continued for two weeks, after which morphine was abruptly and completely withdrawn for 40 hours (control

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withdrawal). Abstinence was then relieved by the administration of morphine and the patients were continued on their previous dosage régime of morphine for at least 10 days. Abrupt withdrawal was repeated, and either cortisone or ACTH was given during the second abstinence period (test withdrawal). Morphine was again administered to relieve abstinence and was continued at the previous stabilization level for an additional four days, when the experiment was terminated (figure 1). When ACTH was

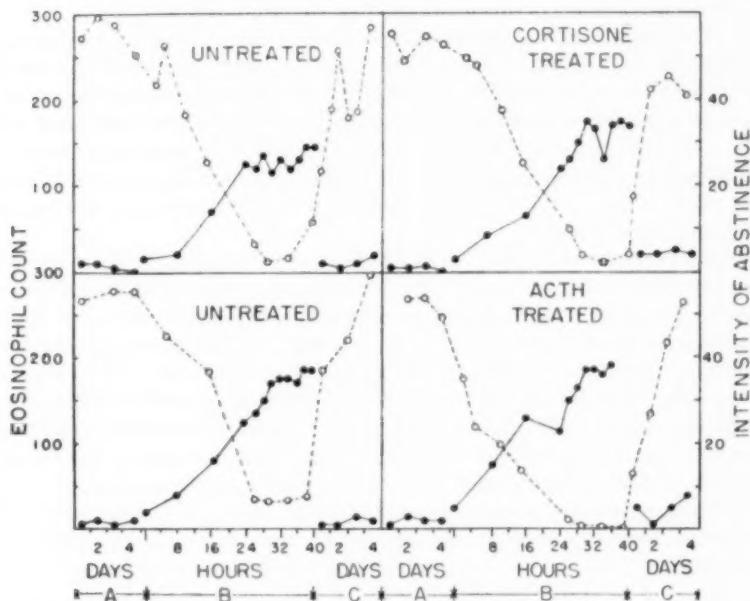


FIG. 1. Shows the average intensity of abstinence symptoms (solid circles, solid lines) and the average eosinophil counts (open circles, dotted lines) of patients untreated during acute morphine abstinence as compared with those of patients treated with cortisone or ACTH. Note inverse relationship of intensity of abstinence to the eosinophil count, and also note that administration of cortisone and ACTH had no ameliorating effect on symptoms of abstinence.

Period A, last four days of administration of morphine; Period B, 40 hour period of abstinence from morphine (note change in time scale); Period C, four days of re-administration of morphine.

used, the withdrawal period from morphine was 36 hours instead of 40 hours.

When this general plan—using a patient as his own control, maintaining the daily dosage of morphine constant, and withdrawing morphine abruptly—was followed, the morphine abstinence syndrome was a very reproducible phenomenon. The same patient has the same symptoms and in the same intensity during repeated withdrawals. Under these circumstances, dependable results can be obtained using very few patients.

Observations: These were made three times daily during stabilization and during the first 24 hours of withdrawal. From the twenty-fourth to the fortieth hour of withdrawal observations were made every two hours. The nonmeasurable symptoms recorded included yawning, lacrimation, rhinorrhea, perspiration, pupillary size, tremor, gooseflesh, restlessness and emesis. Quantitative observations included rectal temperature, respiratory rate, systolic and diastolic blood pressure, weight (once daily) and caloric intake daily. The intensity of abstinence from morphine was quantified according to an hourly point score devised by Himmelsbach.⁵

Eosinophil Counts: These served as an index of the adrenal-cortical response. The technic of eosinophil counting used was that described by Thorn and his co-workers.⁶ The Randolph⁷ technic was employed as a check on the Thorn acetone-eosin method, and the results compared very well. Eosinophil counts were made from one to two hours after breakfast at intervals of two days during maintained addiction to morphine. Counts were made at 8 a.m., 11 a.m., 4 p.m. and 9 p.m. one day before, during, and one day after withdrawal.

Cortisone and ACTH Treatment During Withdrawal: Five subjects, who had been stabilized on 120 to 240 mg. of morphine sulfate daily, received cortisone acetate * which was administered intramuscularly in a dose of 150 mg. every 12 hours, the first dose being given 12 hours prior to morphine withdrawal. Treatment was continued until a total of 600 mg. had been given. Three subjects who had been stabilized on 240 to 300 mg. of morphine sulfate daily received ACTH (Armour Laboratories, Standard LA-I-A) intramuscularly in doses of 25 mg. every six hours until a total of 200 mg. had been administered. One subject who had been stabilized on 600 mg. of morphine daily received 50 mg. doses of ACTH and a total of 400 mg. ACTH therapy was started 18 hours prior to withdrawal and continued until the above total dose had been given in all four cases.

RESULTS

Figure 1 demonstrates that the morphine abstinence syndrome in these patients was not benefited by either cortisone or ACTH. In the experiment with ACTH symptoms appeared earlier, and the patients complained so bitterly that the experiment had to be terminated after 36 hours of abstinence instead of after 40 hours, as planned.

During control withdrawals, the eosinophil count began to drop as soon as significant morphine abstinence symptoms developed, and when abstinence symptoms reached maximal intensity, the average eosinophil count approximated zero. When abstinence was terminated by administration of morphine, the eosinophil count promptly recovered (figure 1).

The activity of the ACTH used in this experiment was demonstrated

* Cortisone acetate supplied through the courtesy of Dr. R. A. Peterman, Merck & Company, Inc.

by the following observations: (1) The patient who received doses of 50 mg. and a total of 400 mg. of ACTH developed a typical "moon facies," which subsided rapidly when ACTH was discontinued. (2) A single dose of 50 mg. of ACTH reduced the eosinophil count from 150 to 37 in 13 hours while this patient was receiving morphine.

In addition to the experiment reported above, two patients have been treated with another sample of ACTH.[†] One of these patients was stabilized on 240 mg. and the other on 300 mg. of morphine daily. One patient received a total of 425 mg. of ACTH, which was given intramuscularly in eight doses of 50 mg. at six-hour intervals, and a final dose of 25 mg., which was administered by intravenous drip over a period of six hours. The other patient received a total of 125 mg. of ACTH in 25 mg. doses. Two of these doses were administered by a slow intravenous drip. The results with this sample of ACTH were the same as those above reported, i.e., symptoms appeared earlier and the patients complained more than during untreated withdrawals.

DISCUSSION

Winter and Flataker⁸ have reported that cortisone and ACTH markedly reduced the effect of morphine and methadone on the tail-flick response to thermal stimuli in normal and spinal rats. They also showed that cortisone was synergistic with a morphine antagonist (N-allylnormorphine). Wikler and associates⁹ have reported that N-allylnormorphine precipitates an abstinence syndrome within 15 minutes when it is given to patients actively addicted to morphine. Therefore, since cortisone counteracts the effects of morphine and has a synergistic action with N-allylnormorphine, one might anticipate that cortisone would cause abstinence symptoms to appear earlier and to be more intense. The results obtained in these experiments support this hypothesis.

The eosinophil response during abstinence from morphine suggests that the pituitary-adrenal mechanism is mobilized by the stress of withdrawal just as it is by other types of stress. Although the pituitary-adrenal response may be necessary for survival of the individual during the stress of abstinence, the experiments show that administration of adrenal hormones in excess of those already being produced by the addict's adrenals has no ameliorating effect on the acute symptoms resulting from withdrawal of morphine.

It is possible that ACTH or cortisone might be of benefit in combating such symptoms of morphine abstinence as anorexia and lethargy when they are present one to three weeks after narcotics have been discontinued. We have performed no experiments of this type, and our results should be interpreted only with respect to the inefficacy of cortisone and ACTH in relieving the acute symptoms of morphine abstinence.

[†] ACTH supplied through the courtesy of Dr. Robert J. Feldman, Armour Laboratories.

CONCLUSIONS

Cortisone and ACTH failed to relieve the acute symptoms of abstinence from morphine.

BIBLIOGRAPHY

1. Rowe, A., Jr., Lamb, G. R., Taylor, F. B., and Insell, L. W.: Experience with ACTH and cortisone in private practice, California Med. **75**: 11, 1951.
2. Boswell, W. H.: Narcotic addiction, U. S. Armed Forces M. J. **2**: 1347-1351, 1951.
3. Hogness, J.: Role of ACTH in narcotic addictions, The Armour Laboratories ACTH Conference **2**: 480-488 (April) 1952.
4. Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Jr., Roche, M., Straehelin, D., and Wilson, D. L.: Usefulness of ACTH and cortisone, New England J. Med. **242**: 865-872, 1950.
5. Himmelsbach, C. K.: Studies of certain addiction characteristics of dihydromorphine, dihydrodesoxymorphone-D, dihydrodesoxycodeine-D, and methyldihydromorphinone, J. Pharmacol. and Exper. Therap. **67**: 239, 1939.
6. Thorn, G. W., Forsham, P. H., Prunty, F. T. G., and Hills, A. G.: A test for adrenocortical insufficiency, J. A. M. A. **137**: 1005, 1948.
7. Randolph, T. G.: Differentiation and enumeration of eosinophils in the counting chamber with a glycol stain; a valuable technic in appraising ACTH dosage, J. Lab. and Clin. Med. **34**: 1696, 1949.
8. Winter, C. A., and Flataker, L.: The effect of cortisone, desoxycorticosterone and ACTH upon the responses of animals to analgesic drugs, J. Pharmacol. and Exper. Therap. **101**: 93-105, 1951.
9. Wikler, A., Carter, R. L., Fraser, H. F., and Isbell, H.: Precipitation of abstinence syndromes by single doses of N-allylnormorphine in addicts, Federation Proc. **11**: 402, 1952.

HYPERTROPHIC OSTEOARTHROPATHY IN PULMONARY MALIGNANCIES*

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INTRODUCTION

HYPERTROPHIC osteoarthropathy has interested internists since the latter part of the Nineteenth Century, when Marie¹ and Bamberger² independently reported the presence of osteitis of the long bones of the extremities associated with pulmonary disease. Since that time, similar bone changes have been reported in many disease processes.

Although chronic pulmonary disease^{3, 4, 5, 6, 7} has been the most frequent cause of osteoarthropathy, these bone changes have been frequently noted in cases of congenital heart disease,^{4, 13} arteriovenous fistula and subacute bacterial endocarditis¹⁴; less frequently it has been described in cases of chronic liver disease,⁴ chronic infections of the intestinal tract,¹⁵ myxedema,⁴ polyposis, aortic aneurysms, carcinoma of nasopharynx,¹⁰ carcinoma of thymus,¹² leukemia and blastomycosis of lung.¹⁰

The gross pathologic process in osteoarthropathy is essentially one of proliferative subperiosteal osteitis surrounding the shaft of the bone. The long bones (tibia, fibula, radius, ulna, femur and humerus) are the ones primarily involved, but in advanced cases the clavicle, rib, scapula and vertebrae may become involved.

There is a proliferation both of the soft tissues and of bone. The periosteum is infiltrated by lymphocytes, plasma cells and leukocytes and becomes considerably thickened. Osteoid matrix is formed from the periosteum which develops into a layer of new bone. These changes can usually be demonstrated by roentgenograms, as figure 1 indicates. The new subperiosteal bone formation is from 1 to 5 mm. thick in most instances and has a thin cortex surrounding the new cancellous bone. This new bone is soft and very vascular, and can be easily stripped from the old cortex.

Among cases secondary to chronic pulmonary infection, Locke¹¹ found that "while at first the new subperiosteal bone is sharply differentiated from the old shaft, at a later period, that is, usually after a lapse of two or three years, the two become more or less fused and in most places are indistinguishable."

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Gall, Bennett and Bauer¹⁶ have recently presented a very complete pathologic study of osteoarthropathy. Their findings showed the distal third of the long bones to be involved initially, with progression toward the proximal portions of these bones. Later they found involvement of the shafts of the metacarpals and metatarsals. It was also their experience that the periosteal changes were greater on the dorsal and medial surfaces.

Although, symptomatically, regression of the osteoarthropathy frequently occurs, there have been only a few cases in which roentgenographic evidence of resorption of the newly formed bone has occurred. However, there is frequently a decrease in the soft tissue swelling around the joints as the



FIG. 1. X-ray of tibia and fibula. Note periosteal thickening of tibia.

primary disease improves. The joints may be primarily involved with thickening of the periarticular tissues, with effusion into the joint and even with erosion of the cartilage.

Clubbing of the fingers is present in practically all cases of pulmonary osteoarthropathy, and although the exact relationship of these two processes is not clear, their frequent association indicates a parallel pathogenesis. There are many who believe hypertrophic osteoarthropathy is an advanced stage of clubbed fingers. In clubbed fingers the change is due to connective tissue thickening, with no change in the terminal phalanges until late, when there is absorption of the bone, and in advanced cases only the base of the terminal phalanx remains.

Many theories as to the causative factors in pulmonary osteoarthropathy have been presented in the medical literature, but none has satisfactorily explained this interesting phenomenon. Attempts to reproduce these bone changes experimentally have been unsuccessful. Injection of purulent secretions from lung abscesses,² production of abscesses by implanting paraffin into the lungs,¹⁰ the intravenous administration of various organisms,¹⁷ and the production of bronchial obstruction in animals¹⁸ have all failed to produce hypertrophic osteoarthropathy. Mendlowitz and Leslie¹⁹ were able to produce hypertrophic osteoarthropathy in one of four dogs by creating an anastomosis between the left pulmonary artery and the left auricular appendage, thereby simulating congenital heart disease with cyanosis. Osteoarthropathy has been described in dogs with tuberculosis^{20, 21} and with bronchogenic carcinoma.²²

Campbell, Sacasa and Camp²³ suggested that osteoarthropathy and clubbing of the fingers were the result of reduced oxygen tension in the circulating blood of the extremities. Mauer²⁴ also suggested peripheral arterial anoxia due to an alteration in stability of the red cell suspension. Others have proposed reduced pulmonary aeration with low oxygen saturation as the cause. These theories are difficult to accept, however, in view of the small volume of lung involved in bronchogenic carcinoma, and the prompt reversal of the process in many cases following pneumonectomy.

The most recent reports in regard to pathogenesis have suggested some endocrine factor. Fried²⁵ postulated dyspituitarism as a probable cause, and presented four cases that developed acromegalic features. In the three cases studied post mortem, pituitary hyperplasia of the eosinophilic cells was demonstrated. Bloom²⁶ recently reported a case in which metastases were found in the anterior pituitary from an adenocarcinoma of the lung, and he suggested that the stimulated pituitary probably was the cause of the osteoarthropathy. Gynecomastia is frequently encountered in cases of pulmonary osteoarthropathy, and this also indicates the presence of some endocrine dysfunction. As Fried²⁵ aptly stated, "Apparently the functions of the lungs are multiple, and their interrelation with other organs, particularly of internal secretion, is complex and worthy of further study." The demonstration of the reversible nature of pulmonary osteoarthropathy as noted in some cases following pulmonary resection indicates that in most instances the underlying causative factor arises from the lungs.

OBSERVATIONS

The purpose of this study of carcinoma of the lung was to determine whether there was any relationship between osteoarthropathy and the type and location of the pulmonary malignant lesion. The cases of carcinoma of the lung selected were restricted to those autopsied, to those subjected to pulmonary resection, and to those cases in which the histopathology and location of the tumor were clearly established clinically. This was done

because of the difficulty in determining accurately the location of the carcinoma from clinical studies alone. Therefore, only 139 cases were selected from approximately 200 cases of carcinoma of the lung diagnosed at the Medical College of Virginia Hospital and the McGuire Veterans Administration Hospital during the five-year period of 1945 to 1951.

Among these 139 cases of carcinoma of the lung, there were 14 cases of acute pulmonary osteoarthropathy. In all 14 cases the initial complaint was referable to the painful joints. However, in five cases cough developed within three months of the bone pains. In three cases pain in the chest had developed by the time of admission to the hospital. The joints involved were the knees, ankles, elbows, wrists and phalanges; these joints were about equally involved among the 14 cases. In all cases, roentgenograms of the involved joints revealed periosteal changes characteristic of osteoarthropathy. Clubbing of the fingers was present in all 14 cases, and in several there was moderate pain associated with this clubbing. It has been our experience that hypertrophic osteoarthropathy and clubbing of the fingers are asymptomatic in cases associated with chronic pulmonary suppuration and in congenital heart disease. In contrast, there is usually considerable pain when the associated disease is carcinoma of the lung. It is probable that in this latter process the periosteal changes are more acute and the proliferation is more rapid. In fact, the term *acute* pulmonary osteoarthropathy would be a more appropriate descriptive term.

The location of the carcinoma was described as either central or peripheral. If the lesion involved either the major or segmental bronchi, it was classed as a central lesion, whereas lesions that involved the small bronchi and were well circumscribed in roentgenograms were classed as peripheral lesions.

Among the 14 cases of osteoarthropathy, the tumor was located peripherally in all but one case. In two of the cases a major bronchus was secondarily involved, but in each the primary tumor appeared to arise from a small bronchus and to have extended by continuity to the major bronchus. In none of the 14 cases was the lesion visible bronchoscopically when first examined. Figure 2 shows the location and relative size of the malignant lesion in each of the 14 cases.

There apparently was no relation between the type of the tumor cells and the osteoarthropathy. The histopathology of these 14 cases was as follows:

Squamous cell, eight cases.

Adenocarcinoma, three cases.

Undifferentiated, one case.

Rhabdomyosarcoma, one case. (Twenty-four months following pneumonectomy the patient is well and there is no evidence of any primary site other than lung.)

Metastatic fibrosarcoma, one case.

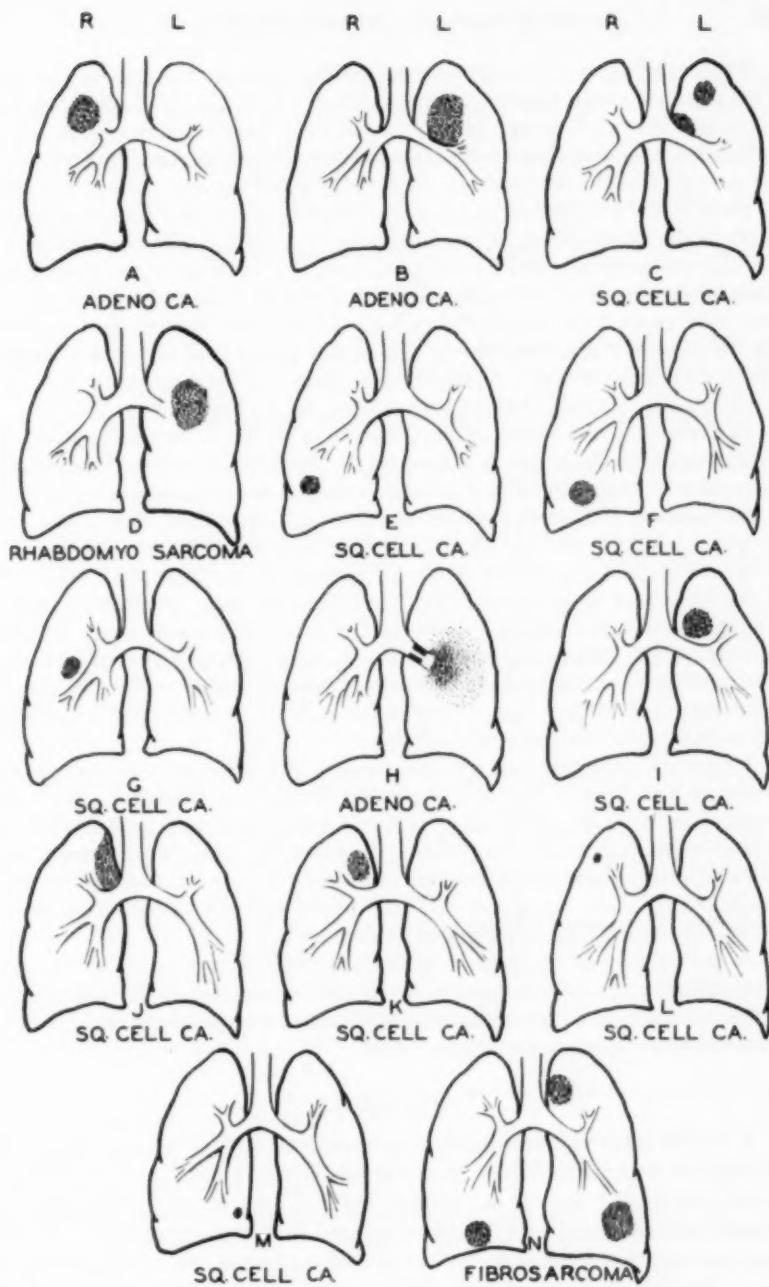


FIG. 2. Artist's drawing of location and relative size of pulmonary malignancies. Type of malignancy is noted in each case.

There also appeared to be no relationship between the size of the carcinoma and osteoarthropathy. Although in the majority of cases the tumor was over 4 cm. in diameter, in several cases the tumor was less than 2 cm. in diameter. In one case of osteoarthropathy the initial chest films revealed only a suspicious density that became definite on subsequent roentgenograms.

Each of the 139 cases was studied to determine whether infection played a part in the development of osteoarthropathy. Of the 139 cases, infection was obvious clinically and histologically in 57; in three there were large abscesses present, and in two the carcinoma was in a lung cyst. In none of these cases was there osteoarthropathy. In 61 cases infection, if present, was not clinically apparent, and it was in this group that all cases of osteoarthropathy were found. It is therefore apparent that infection plays no significant rôle in the development of these bone changes.

In reviewing the literature regarding hypertrophic osteoarthropathy in carcinoma of the lung, one is impressed by the predominance of peripheral pulmonary lesions. In 1951 Pattison, Beck and Miller²⁷ reported six cases of carcinoma of lung with osteoarthropathy, and in none of these cases was the lesion visible bronchoscopically; five of the cases were obviously peripherally located, and the other was located apparently in a secondary bronchus. Of the four cases reported by Fried²⁸ in 1943, two were peripheral and two involved main stem bronchi. Two cases of osteoarthropathy from the Case Records of the Massachusetts General Hospital revealed peripheral pulmonary lesions, one an adenocarcinoma²⁹ and the other a fibrosarcoma²⁹ of the lung. Fischl's³⁰ case of osteoarthropathy reported in 1950 was likewise a peripheral carcinoma of the lung.

Peripheral carcinoma of the lung was also the lesion described in the reports of Van Hazel⁷ and of Temple and Jaspis.³¹ Holmes, Bauman and Ragan³² in 1950 described seven cases of pulmonary osteoarthropathy associated with pulmonary neoplasm. In five cases the clinical summaries indicated a peripheral location of the neoplasm, in one the data given were insufficient to allow an opinion as to location, and the seventh case was a "giant cell tumor" that metastasized to the lung.

A review of the reported cases of osteoarthropathy in regard to the histopathology of the pulmonary malignant lesions failed to indicate the predominance of any type, although adenocarcinoma was about as frequently encountered as squamous cell carcinoma.

SUMMARY

Fourteen cases of osteoarthropathy associated with malignant disease of the lung are reported. In 13 cases the tumor was located in the periphery of the lung. The size of the tumor and the type of malignant cells apparently played no rôle in the development of osteoarthropathy. It was also apparent that pulmonary infection had no part in the pathogenesis of osteoarthropathy associated with pulmonary malignant disease.

BIBLIOGRAPHY

1. Marie, P.: De l'osteo-arthropathie hypertrophiante pneumique, *Rev. de méd.*, Paris **10**: 1-36, 1890.
2. Bamberger, E.: Ueber Knochenveränderungen bei chronischen Lungen- und Herzkrankheiten, *Ztschr. f. klin. Med.* **18**: 193, 1891.
3. Berg, R., Jr.: Arthralgia as a first symptom of pulmonary lesions, *Dis. of Chest* **16**: 483, 1949.
4. Cushing, E. H.: Clubbed fingers and hypertrophic pulmonary osteoarthropathy, *Internat. Clin.* **2**: 200, 1937.
5. Kessel, L.: The relation of hypertrophic osteoarthropathy to pulmonary tuberculosis, *Arch. Int. Med.* **19**: 239, 1917.
6. Mendlowitz, M.: Clubbing and hypertrophic osteoarthropathy, *Medicine* **21**: 269, 1942.
7. Van Hazel, W.: Joint manifestations associated with intrathoracic tumors, *J. Thoracic Surg.* **9**: 495, 1940.
8. Kaplan, R. H.: Clubbed fingers in pulmonary tuberculosis, *Am. Rev. Tuberc.* **44**: 439, 1941.
9. Shaw, H. B., and Cooper, R. H.: Pulmonary hypertrophic osteoarthropathy occurring in a case of congenital heart disease, *Lancet* **1**: 880, 1907.
10. Compere, E. L., Adams, W. E., and Compere, C. L.: Generalized hypertrophic pulmonary osteoarthropathy, *Surg., Gynec. and Obst.* **61**: 312, 1935.
11. Locke, E. A.: Secondary osteoarthropathy and its relation to simple clubbed fingers, *Arch. Int. Med.* **15**: 659, 1915.
12. Miller, E. R.: Carcinoma of the thymus with marked pulmonary osteoarthropathy, *Radiology* **32**: 651, 1939.
13. White, P. D., and Sprague, H. B.: The tetralogy of Fallot, *J. A. M. A.* **92**: 787, 1929.
14. Cotton, T. F.: Clubbed fingers as a sign of subacute infective endocarditis, *Heart* **9**: 347, 1922.
15. Schlicke, C. P., and Bargen, J. A.: Clubbed fingers and ulcerative colitis, *Am. J. Digest. Dis.* **7**: 17, 1940.
16. Gall, E. A., Bennett, G. A., and Bauer, W.: Generalized hypertrophic osteoarthropathy, *Am. J. Path.* **27**: 349, 1951.
17. Phemister, D. B.: Chronic lung abscess with pulmonary hypertrophic osteoarthropathy, *Surg. Clin. Chicago* **1**: 381-389, 1917.
18. Harter, J. S., and Churchill, E. D.: Quoted by Compere, Adams and Compere, *Surg., Gynec. and Obst.* **61**: 312, 1935.
19. Mendlowitz, M., and Leslie, A.: Experimental simulation in the dog of cyanosis and hypertrophic osteoarthropathy, *Am. Heart J.* **24**: 1941, 1942.
20. Hebrant, A., and Liegedis, O.: Bull. Acad. roy. de méd. de Belgique **8**: 275, 1928.
21. Ball, V., and Alamartine, H.: Tuberculose inflammatoire et ostéo-arthropathies hypertrophiantes pneumiques, *Gaz. d. hôp., Paris* **85**: 1587-1590, 1912.
22. Wissing, E. G., and Weiss, L.: Unusual case of pulmonary osteoarthropathy in a dog, *Am. J. Roentgenol.* **50**: 527, 1943.
23. Campbell, D. C., Sacasa, C. F., and Camp, J. D.: Chronic hypertrophic osteoarthropathy, *Proc. Staff Meet., Mayo Clin.* **13**: 708, 1938.
24. Mauer, E. F.: On etiology of clubbing of the fingers, *Science* **104**: 555, 1946.
25. Fried, B. M.: Chronic pulmonary osteoarthropathy; dispituitarism as a probable cause, *Arch. Int. Med.* **72**: 565, 1943.
26. Bloom, W.: Pituitary implications in hypertrophic pulmonary osteoarthropathy, *Ann. Int. Med.* **29**: 361, 1948.
27. Pattison, J. D., Jr., Beck, E., and Miller, W. B.: Hypertrophic osteoarthropathy in carcinoma of the lung, *J. A. M. A.* **146**: 783, 1951.

28. Cabot Case 34481, New England J. Med. **239**: 834, 1948.
29. Cabot Case 31271, New England J. Med. **233**: 18, 1945.
30. Fischl, J. R.: Severe hypertrophic pulmonary osteoarthropathy, Am. J. Roentgenol. **64**: 42, 1950.
31. Temple, N. L., and Jaspin, G.: Hypertrophic osteoarthropathy, Am. J. Roentgenol. **60**: 232, 1948.
32. Holmes, H. H., Bauman, E., and Ragan, C.: Symptomatic arthritis due to hypertrophic osteoarthropathy in pulmonary neoplastic disease, Ann. Rheumat. Dis. **9**: 169, 1950.

MORTALITY, MORBIDITY AND TREATMENT OF MYOCARDIAL INFARCTION: A REVIEW OF 455 CASES *

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DURING the past several years, numerous studies have appeared in the medical literature regarding the treatment of acute myocardial infarction. Mortality rates in this condition have been reported as varying from 81 per cent⁷ to 50 per cent,⁸ while the incidence of embolic phenomena is stated to vary from 1 per cent to 37 per cent. The use of anticoagulant therapy has been enthusiastically advocated by Wright,¹ Nichol and Page² and Parker and Barker.³ Other, more conservative investigators^{4, 5, 6} deny the need for routine use of anticoagulants in acute myocardial infarction.

The practicing physician cannot help but be bewildered by these contradictory reports, and yet such studies are necessary for a final evaluation of any therapeutic program.

It is difficult to make comparisons of statistical reviews. The reason for the wide variation in results is due in part to the fact that different types of patients are being studied by different investigators. In some groups only patients with their first attack of myocardial infarction are presented; in other groups only men of military age are studied, while in other discussions any infarction up to six weeks of age has been included in mortality figures. Other factors, such as complications in each individual case, play an important rôle in molding a final conclusion. For these reasons, it is not our purpose to compare this series with any other. We had no preconceived notion as to what the results would reveal but were interested in the progress of a group of patients treated in one hospital, with a wide distribution of age and sex, with the usual complications and under close observation.

SELECTION OF PATIENTS

This study includes all patients admitted to the Evanston Hospital from January 1, 1946, to January 1, 1951, with a proved diagnosis of acute myocardial infarction. No case was included unless the electrocardiogram revealed the characteristic changes or unless the diagnosis was proved at postmortem examination. Four hundred fifty-five patients were studied. If it appeared from the history that the onset of the infarction had occurred more than 72 hours previous to admission to the hospital, the patient was not included in this report. Such a restriction was made in order to ex-

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clude as completely as possible those patients who actually were recovering from their cardiac insult before treatment was instituted. Patients who died within 24 hours of admission were not included, since it is unlikely that any form of therapy would be life-saving to those dying so quickly following the acute attack. The discussion on anticoagulant therapy refers to patients treated with heparin and Dicumarol, or Dicumarol alone.

In classifying arrhythmias, no case was included unless the arrhythmia was proved by electrocardiographic evidence.

The diagnosis of cardiac failure was made by clinical findings and included those patients with signs and symptoms indicating definite myocardial insufficiency, such as marked dyspnea, pulmonary congestion, acute pulmonary edema, hepatomegaly and other signs of elevated venous pressure.

RESULTS

Total Mortality: The mortality rates have been calculated for this entire group as well as for those patients suffering their first attack of myocardial infarction, and for those suffering from more than one attack. The results are presented in tables I through 3.

TABLE I
Total Mortality

Number of Patients	Lived	Died	Mortality %
455	275	180	39.5

TABLE II
Mortality of First Attack

Number of Patients	Lived	Died	Mortality %
390	255	135	34.6

TABLE III
Mortality of Group Suffering from More than One Attack

Number of Patients	Lived	Died	Mortality %
65	20	45	69.2

Sex and Age: Of the patients studied, there were 297 males and 158 females. Fifty per cent of the males and 56.3 per cent of the females died. The incidence of women in the present series compares closely with the 2.2 to 1 ratio of Mintz and Katz,⁸ but is at variance with the sex incidence

TABLE IV
Distribution by Age

Decades	Living	Dead	Total
30-40	3	3	6
40-50	46	6	52
50-60	90	23	113
60-70	83	45	128
70-80	65	60	125
80-90	15	19	34
90-100	1	2	3

as reported by other authors,^{9, 10, 11} who found a much lower incidence of females in their respective series. The distribution by age is to be found in table 4.

Location of Infarct: The locations of the myocardial infarctions as determined by electrocardiography and postmortem examination are tabulated in table 5.

TABLE V
Locations of Infarcts

	Living	Dead	Total
Posterior	114	30	144
Anterior	135	44	179
Ant. subendocardial	15	2	17
Post. subendocardial	3	3	6
Post. lateral	12	5	17
Post. septal	4	15	19
Ant. lateral	2	6	8
Extensive post. and ant.	4	6	10
Ant. septal	6	28	34
Septal	0	4	4
Unidentified	7	11	18

ANTICOAGULANT THERAPY

Effect on Mortality: The effect of anticoagulants on the mortality rates for the groups previously presented is tabulated in tables 6 through 9.

From these figures it is obvious that anticoagulant therapy produced a definite improvement in prognosis and corresponds closely to the figure reported by Wright¹ and his group. Since ours was an unselected group, with patients of all ages and with various complications in both the treated

TABLE VI
Effect of Anticoagulants on Mortality of Patients Suffering First Attack

Number of Patients	Lived	Died	Mortality %
140	113	27	19.2

TABLE VII
Mortality of Patients Suffering First Attack Who Did Not Receive Anticoagulants

Number of Patients	Lived	Died	Mortality %
250	142	108	43.0

TABLE VIII
Effect of Anticoagulants on Mortality of Patients Suffering More than One Attack

Number of Patients	Lived	Died	Mortality %
16	11	5	31.2

TABLE IX
Mortality of Patients Suffering More than One Attack
Who Did Not Receive Anticoagulants

Number of Patients	Lived	Died	Mortality %
49	9	40	81.6

and untreated group, one cannot escape the conclusion that anticoagulant therapy was an extremely valuable therapeutic agent in this series.

The adequacy of Dicumarol control has been studied. Criteria for control were determined as follows:

1. Good control—prothrombin time 20 to 30 per cent of normal.
2. Fair control—prothrombin time 30 to 40 per cent of normal.
3. Poor control—prothrombin time above 40 per cent of normal.

Of the 124 patients who received Dicumarol and lived, 76.6 per cent had prothrombin times consistently below 40 per cent of normal. Of the 32 patients who received Dicumarol and died, 68 per cent had prothrombin times consistently below 40 per cent of normal. These figures mean that in the group that lived the prothrombin control was somewhat better than in the group that died, but actually the figures cannot be considered statistically significant as the number of patients is too small.

THROMBOEMBOLIC PHENOMENA

Of the total number of patients who received anticoagulant therapy, 7.23 per cent developed thromboembolic complications. Of the patients who did not receive Dicumarol, 15.60 per cent developed thromboembolic complications. The incidence of this type of complication in our series is lower than in groups reported by Nay and Barnes,¹² who found 37 per cent of patients developed embolic complications if not treated with anticoagulants. In Wright's¹ study, 26 per cent of untreated patients developed clotting abnormalities, while 10.9 per cent of the treated group presented an embolic problem. In the study reported by Barnum,¹¹ no anticoagulant therapy was used and the incidence of thromboembolism was only 5.9 per cent.

In our group, of the total number of patients who received anticoagulant therapy, 15.21 per cent revealed evidence of abnormal bleeding. This included microscopic hematuria in patients whose urine had been normal previous to receiving Dicumarol. In this group the highest prothrombin level at which bleeding occurred was 46 per cent, and the lowest level was 13 per cent. In no case was bleeding of a serious nature.

ARRHYTHMIAS

Table 10 summarizes the mortality rates of the various arrhythmias encountered in this study.

Fifty per cent of the patients who developed an arrhythmia other than sinus tachycardia died. The mortality rate of 63 per cent in the group that developed auricular fibrillation emphasizes the seriousness of this type of rhythm following myocardial infarction. Other authors^{13, 14} have also indicated the grave nature of this complication.

TABLE X
Mortality of Various Arrhythmias

Type of Arrhythmia	Total Number of Patients	Number of Patients Who Died	Mortality Per Cent
Auricular fibrillation	52	33	63%
Supraventricular tachycardia	6	1	16%
Auricular flutter	6	3	50%
Ventricular tachycardia	7	5	71%
Paroxysmal auricular tachycardia	9	5	55%
Partial AV block	7	5	71%
Complete AV block	4	3	75%

HEART FAILURE

Congestive heart failure developed in 121 patients. Table 11 presents the effect of digitalis therapy in this group.

Although this group is small, it emphasizes the grave prognostic import of heart failure following myocardial infarction. We feel that when heart failure is present, digitalis should be administered with careful supervision.

TABLE XI
Effect of Digitalis on Mortality Rate

Digitalis	Lived	Died	Mortality Per Cent
89	25	64	71.9
No Digitalis	Lived	Died	Mortality Per Cent
29	6	23	79.3

DISCUSSION

The results of this study convey the impression that anticoagulant therapy is of value in reducing the mortality rate and incidence of thromboembolic complications in acute myocardial infarction. Although our series does not lend itself to statistical evaluation, because of lack of a control group, we feel that the results are significant since this group of patients represents an adequate sample of any coronary hospital population.

The antagonists of anticoagulant therapy agree that there are certain indications for this type of treatment.^{6,7,9} These are generally considered to occur in the more severely ill group, those having had a previous infarct, those in shock or in heart failure or manifesting other complications. We certainly agree with these indications, but we do not feel that anticoagulant therapy should be withheld until complications occur. When the patient is first seen during the acute attack, no one can predict what the next few hours or days will bring. Yet it is at this time that the formation of a mural thrombus begins, and for this reason we feel that the patient should receive the possible benefits of anticoagulant therapy when the diagnosis is first suspected. After the course of the illness has been well established and it is certain that serious complications will not ensue, the attending physician may at his discretion discontinue such treatment. With adequate

laboratory control, which is essential, the dangers of serious bleeding do not appear to outweigh the usefulness of this form of treatment. We do not wish to advocate routine use of any therapy; but we do wish to advocate the routine consideration of all forms of useful therapy in each individual patient.

SUMMARY

A study of 455 patients suffering from acute myocardial infarction is presented. The results are as follows:

1. The mortality rate for the entire group was 39.5 per cent.
2. The mortality rate for patients suffering from their first attack was 34.6 per cent.
3. The mortality rate for patients suffering from more than one attack was 69.2 per cent.
4. There were 297 males and 158 females in the entire group.
5. The mortality rate for patients suffering from the first attack, who received anticoagulant therapy was 19.2 per cent.
6. The mortality rate for patients suffering from the first attack, who did not receive anticoagulant therapy was 43.0 per cent.
7. The mortality rate of patients suffering from more than one attack, who received anticoagulant therapy was 31.2 per cent.
8. The mortality rate for patients suffering from more than one attack, who did not receive anticoagulant therapy was 81.6 per cent.
9. The incidence of thromboembolic complications in the group of patients who did not receive anticoagulant therapy was 15.6 per cent.
10. The incidence of thromboembolic complications in the group of patients who did receive anticoagulant therapy was 7.23 per cent.
11. Of the patients who received anticoagulant therapy, 15.21 per cent showed some abnormal bleeding. In no case was the bleeding serious.
12. In the group of patients who developed congestive heart failure and did receive digitalis, the mortality rate was 71.9 per cent.
13. In the group of patients who developed congestive heart failure and did not receive digitalis, the mortality rate was 79.3 per cent.
14. The incidence of cardiac arrhythmias and associated mortality is also presented.

BIBLIOGRAPHY

1. Wright, I. S., Marple, C. D., and Beck, D. F.: Anticoagulant therapy of coronary thrombosis with myocardial infarction, *J. A. M. A.* 138: 1074, 1948.
2. Nichol, E. S., and Page, S. N.: Dicumarol therapy in acute coronary thrombosis, *J. Florida M. A.* 32: 365, 1946.
3. Parker, R. L., and Barker, N. W.: The effect of anticoagulants on the incidence of thromboembolic complications in acute myocardial infarction, *Proc. Staff Meet., Mayo Clin.* 23: 367, 1948.
4. Sigler, L. H.: Letter to the Editor, *J. A. M. A.* 145: 1004, 1951.

5. Russek, H. I., Zohman, B. L., White, L. G., and Doerner, A. A.: Indications for bis-hydroxycoumarin (Dicumarol) in acute myocardial infarction, *J. A. M. A.* **145**: 390, 1951.
6. Rytand, D. A.: Anticoagulants in coronary thrombosis with myocardial infarction, *Arch. Int. Med.* **88**: 207 (Aug.) 1951.
7. Master, A. M., Jaffe, H. L., and Dock, S.: Treatment and immediate prognosis of coronary artery thrombosis, *Am. Heart J.* **12**: 547, 1936.
8. Mintz, L. S., and Katz, L. N.: Recent myocardial infarction, *Arch. Int. Med.* **80**: 205, 1947.
9. Parkinson, J., and Bedford, D. E.: Cardiac infarction and coronary thrombosis, *Lancet* **1**: 4, 1928.
10. Mullins, N. L.: Age incidence and mortality in coronary occlusion: a review of four hundred cases, *Pennsylvania M. J.* **39**: 322, 1936.
11. Barnum, D. R., Garr, W. R., Gilbert, N. C., and Fenn, G. K.: Coronary thrombosis treated with xanthines, *Quart. Bull., Northwestern Univ. M. School* **24**: 6, 1950.
12. Nay, R. M., and Barnes, A. R.: Incidence of embolic or thrombotic processes during convalescence from acute myocardial infarction, *Am. Heart J.* **30**: 65, 1945.
13. Askey, J. M., and Neurath, O.: The prognostic significance of auricular fibrillation in association with myocardial infarction, *Am. Heart Jr.* **29**: 575, 1945.
14. Rosenbaum, F. F., and Levine, S. A.: Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction, *Arch. Int. Med.* **68**: 913, 1941.

OBSERVATIONS ON ATHEROSCLEROSIS OF THE CORONARY ARTERIES IN MALES UNDER THE AGE OF 46: A NECROPSY STUDY WITH SPECIAL REFERENCE TO SOMATOTYPES *

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RECENT studies on establishing criteria for the prediction of the development of coronary artery disease, investigations relating to the development of coronary artery disease in certain somatotypes, and reports of serum cholesterol levels, cholesterol/phospholipid ratios, lipoproteins in the form of macromolecules, diet and obesity in relation to the development of coronary artery disease have resulted in what appear to be contradictory data. These studies have also raised many questions concerning the mechanism of development and the problem of prevention and treatment of atherosclerosis of the coronary arteries. On the one hand, there are the proponents of the view that the disturbances in various aspects of cholesterol metabolism are prime factors in the entire problem^{1, 2, 3}; on the other, such observers as Keys⁴ have cast serious doubt upon the validity of the statistics used in support of these views, and still others have not corroborated the above findings at all. The investigation of Gertler and his associates⁵ has raised the question of predetermination by somatotypes in the development of coronary artery disease in certain individuals. Opposed to Gertler's views are those who emphasize the importance of later environmental influences. It is with these and related aspects of the problem that the following study is concerned.

METHODS AND MATERIALS

The study consisted of two groups of cases. In the first group, 38 consecutive necropsies were performed on individuals in whom death had occurred secondary to coronary artery disease (from simple narrowing to practically complete sclerotic or thrombotic occlusion). All of these were adult white males under the age of 46. The cases were limited to those under 46 because, in this age group, hypertension, diabetes and obesity do not play so important a rôle as somewhat later in life. Furthermore, the somatotype of the individual is more clearly defined and not likely to be distorted by the aging process or chronic illness. With few exceptions, these individuals were not under the care of any physician for any known

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From the Medical Examiner's Office of the Department of Laboratory and Research of Westchester County and the Division of Pathology of Grasslands Hospital, Valhalla, New York.

heart ailment. They apparently had considered themselves as healthy and were engaged in their normal occupational and recreational activities immediately prior to the time of death. At necropsy these individuals revealed no organic lesion to account for death other than advanced atherosclerosis in the coronary arteries.

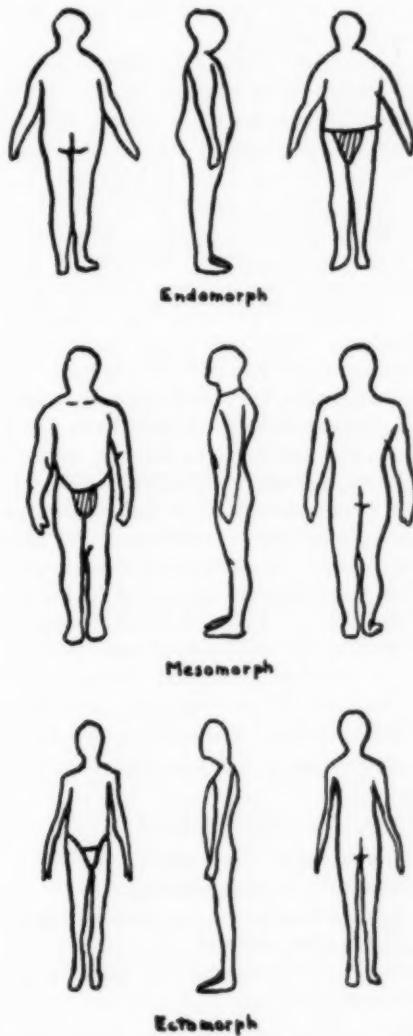


FIG. 1. (Adapted from Sheldon.⁶) Drawings showing extremes of three types of physique.

The second group studied consisted of 73 consecutive necropsies on white adult males under the age of 46 who were, with few exceptions, in apparently good health up to the time of sudden death that resulted either from accident, homicide, suicide or some acute noncardiac condition, such as spontaneous subarachnoid hemorrhage. Except in one instance, these patients had no previous cardiac history. If, at necropsy, evidence of cardiac disease other than that involving the coronary arteries was found, such cases were eliminated from the group to be studied.

Both groups of cases had come under the jurisdiction of the Medical Examiner's Office of Westchester County, which serves a community of 635,000 people. According to the latest census figures, of this 635,000, 100,000 are males between the ages of 20 and 46. Somewhat over 5 per cent of these 100,000 are Negroes, and at least another 5 per cent are of Jewish origin. This community consists of semi-rural, urban and city areas with a moderate number of industrial plants. Again, according to the latest census figures of the employed group of individuals, approximately 20 per cent were in the professional, business and managerial group, 22 per cent clerical, 8 per cent craftsmen, 5 per cent heavy laborers, and 45 per cent service and skilled workers. The cases under the jurisdiction of the Medical Examiner's Office represent a rather fair cross-section of the population and, again with few exceptions, have been long-term residents of the community.

Prior to necropsy, the somatotype of each body was determined according to the classification of Sheldon⁶ into the four major groups, viz., endomorphy, ectomorphy, mesomorphy and mixed. The classification of each case was determined independently by at least two and more often three observers who had familiarized themselves with Sheldon's inspectional criteria. In addition, certain measurements were made as a further guide in classification. The measurements consisted of height, extremity length, estimated weight and shoulder width. Remarkable agreement was achieved by the independent observers. No attempt was made to classify the body types further than by primary dominant characteristics. We were not concerned with the degrees of the secondary and tertiary components of physique, since facilities were not available for this more detailed classification. Some of the inspectional criteria utilized (figure 1) were as follows:

MESOMORPHY

1. Squareness and hardness * of body.
2. Rugged, prominent, massive muscling.
3. Transverse diameter exceeding anterior posterior diameter.
4. Trunk large and heavy muscled.
5. Thoracic volume predominating over abdominal volume.
6. Pelvis sturdy and powerful.
7. Wrist heavy.

* This characteristic obviously could not be determined post mortem.

8. Both arms and legs evenly proportioned as to proximal and distal segments.
9. Relatively sharp inward bowing in the lumbar region.

ECTOMORPHY

1. Linearity, fragility and delicacy of body.
2. Slight, thready muscles.
3. Anterior-posterior diameters extremely reduced.
4. Transverse diameters reduced, but not so sharply as the anterior-posterior diameters.
5. Shoulder droop.
6. Limbs relatively long.
7. Lumbar curve flat and high.
8. Abdomen flat and relatively short, and of shallow depth.
9. Distal segments of extremities relatively long.
10. Neck long and slender.
11. Small facial mass as compared to cranial mass.

ENDOMORPHY

1. Roundness and softness of body.
2. Anterior and posterior diameters and the lateral diameters tend up toward equality.
3. Predominance of abdominal and thoracic volume over extremities.
4. Predominance of abdomen over thorax.
5. Rounding and hamming of thighs and upper arms.
6. Smoothness of contours.
7. No muscle relief.
8. Short tapering limbs.
9. Vertebral column appearing relatively straight.
10. Small bones.

Individuals were placed in the mixed group when none of the previous three types clearly predominated.

Necropsies were then performed and particular attention was directed to the heart, aorta and kidneys. The major coronary arteries in 60 of these cases (111 cases studied) were injected, opened and roentgenograms made according to the Schlesinger⁷ technic. In all of the hearts, the coronary arteries were carefully dissected and the degree of atherosclerosis was plotted. Representative histologic sections were prepared from the segment showing the maximal degree of involvement of each major branch. The degree of coronary atherosclerosis was graded from 0 to 4 plus; 0 indicated either no evidence of sclerosis or a minimal degree of intimal streaking; 4 plus indicated advanced sclerosis, with marked or complete intraluminal obstruction. Heart weights, the degree of atherosclerosis in the aorta and any evidence

of hypertension, either recent or preexisting, as evidenced by arteriolar nephrosclerosis, were carefully noted. The state of nutrition of the individual as revealed by the amount of subcutaneous, mesenteric, omental and other fat deposits was also noted.

Although it was not part of this particular study, the coronary arteries in the young Negro males and white females were also investigated. Brief reference to these will be made later in this report.

ANALYSIS OF INDIVIDUALS DEAD OF CORONARY ARTERY DISEASE

Instances of death secondary to coronary artery disease in this study, although consecutive and not selected, are still not representative of a true cross section of the entire coronary artery disease problem. Since individual cases came under the jurisdiction of the Medical Examiner's Office, they had for the most part no previous history of heart disease or related medical attention. Deaths of individuals with coronary artery disease in the same age group who had been under the care of physicians usually would not be reported to the Medical Examiner's Office. For this reason, patients with long-standing histories of angina or previous known episodes of myocardial infarction are not represented. An excellent detailed and representative picture of this problem was reported by Yater and his associates in a study on 866 cases of coronary artery disease in men 18 to 39 years of age in the Armed Forces of this country.^{8, 9, 10} However, the present study is, in one sense, more representative than Yater's group because it presents the findings in individuals in their usual habitat and activity up to the time of death. Furthermore, these cases were all studied by the same prosector, using the same standards and technics throughout.

An analysis of the various types of physique as determined by Sheldon's criteria in these 38 consecutive necropsied individuals indicated that the mesomorphic group predominated (table 1). The proportion of dominant mesomorphs who died suddenly from coronary artery disease is undoubtedly higher than the percentage of mesomorphs in the general population. Sixty-three per cent of this group were of the mesomorphic somatotype, whereas in the second group of cases studied, where 73 young adults died from accidental, suicide or homicidal cause, only 41 per cent were dominant mesomorphs. Although no data are available as to the somatotype distribution in the general population, this too would appear to be higher than the proportion of mesomorphs seen in the general population. However, there is evidence to indicate that mesomorphs engage more often in those activities that might lead to violent death.¹¹ Only a small number of endomorphs was present in both groups. Gertler and his associates,¹² in clinical studies on young adults with coronary artery disease, also found a definite tendency for dominant mesomorphs with secondary characteristics of endomorphy to predominate.

A further analysis of these 38 cases revealed that seven were unemployed, seven were service workers, nine were heavy laborers, eight were skilled laborers, five were in the professional, business-managerial category, and two were white-collar workers. The previously mentioned general employment distribution in Westchester County reveals that this distribution in individuals who died from coronary artery disease is not significantly different from the general employment picture. However, the small number in this group who were in the professional, business-managerial category is at variance with the observations of Gertler and associates. They reported that the preponderant number of young individuals with myocardial infarction was in this particular occupational category. There has been considerable difference of opinion relative to occupational predisposition in coronary artery disease. Master and Jaffe,¹³ in an analysis of 1,495 cases with coronary occlusion, found no occupational trends. The statistics derived from our group of cases are not necessarily any more valid than those of other groups. They are presented to stress the necessity for caution in arriving at conclusions concerning occupational predisposition. However, in the series of cases reported by Gertler,¹² 59 out of 100 patients were selected by

TABLE I
Body Type and Coronary Deaths

Body Type	Number of Cases
Mesomorph	24
Ectomorph	3
Endomorph	3
Mixed	8
Total	38

physicians and sent from various parts of the country. The cases, therefore, were not consecutive. Because of this method of selecting cases, the group would not be properly representative of all income groups. Generally, only those seen by private cardiologists or those in a position to take time off for a trip to the center of the Gertler study group¹² would fit into their study. A recent study in England¹⁴ of the distribution of coronary artery disease in physicians is worthy of mention because it appears to be a carefully controlled and highly significant study. In this investigation it was noted that general practitioners of medicine had a much greater incidence of coronary artery disease than consultants and specialists.

Another difference between this study and that reported by Gertler and associates¹² was the proportion of the so-called Mediterranean peoples with coronary artery disease. Of the Westchester group, two of the cases were Jewish, whereas in the Gertler series of 100 cases, 27 were Jewish. For this reason, it was intimated that there was a tendency for coronary artery disease to occur more frequently in the group of the Mediterranean peoples among which the Jewish people were classified. Thus, 5 per cent of the cases in our group were Jewish (two out of 38). This is approximately

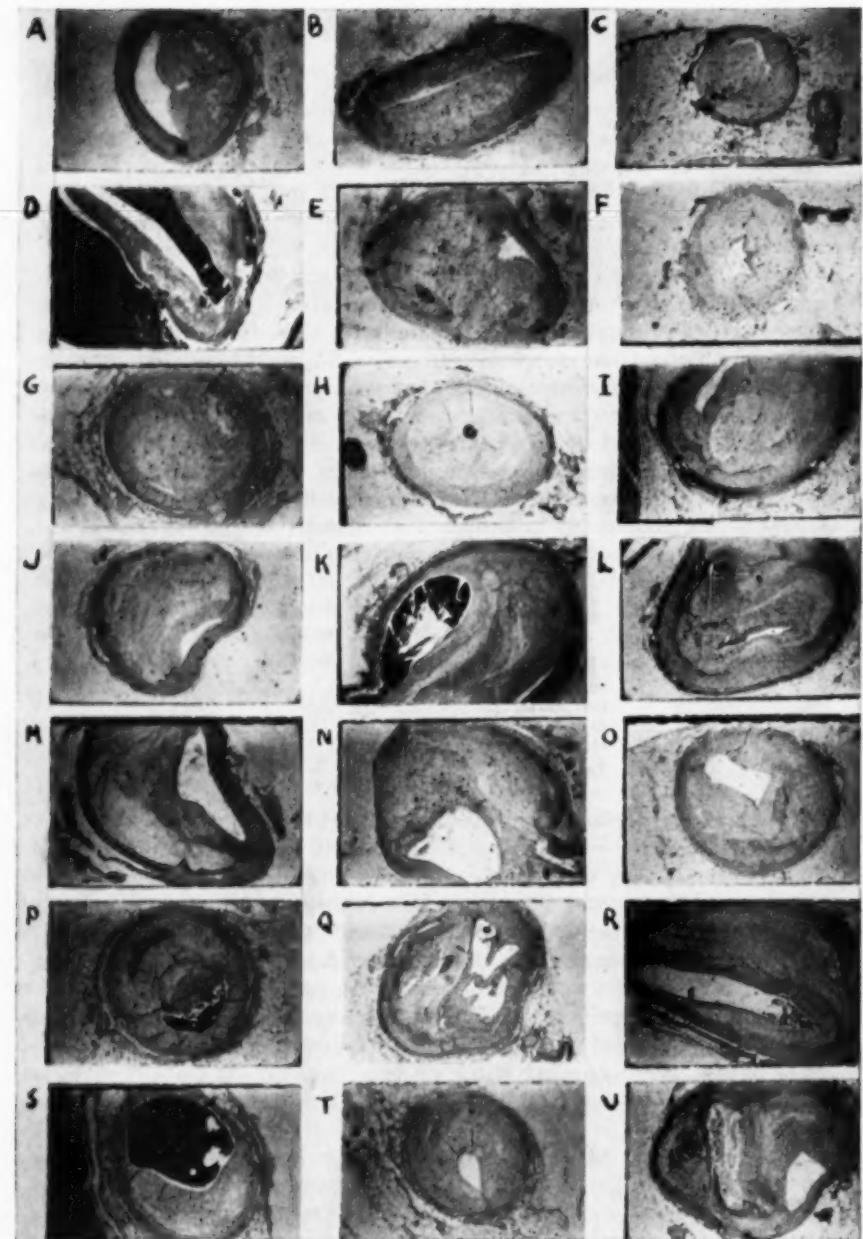


FIG. 2. Photomicrographs of cross-sections of coronary arteries through representative areas of maximal atherosclerosis in 21 individuals dying from coronary artery disease. The material in the lumen is injection mass.

the same proportion as the Jewish population of Westchester County. It would also appear to be unsound practice to classify under one anthropologic heading, as Gertler has done, groups based upon religion and upon national origin. Furthermore, the assumption that the origin of all Jewish people in this country must be in the Mediterranean area is also erroneous, unless one is thinking in very remote historical terms.

In this group of 38 individuals who died of advanced coronary atherosclerosis without any significant previous related history, only five had thrombi (two recent, three old), two had hypertension, five had myocardial infarcts (one recent, four old), and two had a history of angina (three years' and 20 years' duration). On the other hand, the group reported by Gertler usually gave previous histories of varying duration, and usually showed clinical evidence of myocardial infarction.

The anatomic changes in the coronary arteries of these hearts revealed every variation and generally the same distribution seen in coronary artery disease in the older age groups, with the one difference that calcification generally was not so marked (figure 2). Since these were sudden deaths without previous history of disease, the incidence of thrombosis, as indicated previously, was infrequent. This was also true of the incidence of myocardial infarction, because death usually occurred within a few minutes to hours after the attack. Yater and his associates^{8, 9, 10} have demonstrated that the anatomic changes in the group of young individuals with coronary artery disease are no different from those seen in the older age group. Saphir and Gore¹⁵ analyzed some of the youngest cases originally reported by Yater and showed that an underlying inflammation was probably the basis for the development of coronary artery disease in some of these individuals. In the currently reported group of cases, only one had any evidence of a possible underlying inflammatory lesion. This case corresponded to those described by von Albertini as a form of diffuse, stenosing coronary arteritis. Adlersberg¹⁶ reviewed 50 necropsies on young individuals with coronary artery disease at Mount Sinai Hospital over a period of 20 years. In this group he found one with a picture similar to that described by von Albertini.

Although Yater in his extensive study found no case in which advanced arteriosclerosis was limited to one small segment of the coronary arterial tree, two such instances were found in this study. In both cases the arteriosclerosis, even though limited in extent, was so advanced that death resulted from the impingement of the lesion on the lumen of the vessel. Another instance was observed in a female not included in this series. This patient was one of four females without hypertension, diabetes or xanthomatosis under the age of 46 who died of coronary artery disease during the same period of time in which we were able to collect 38 cases in young white males. This 38 year old white female, with no previous medical history relating to heart disease, had an episode of precordial pain at 5:00 a.m. and died within

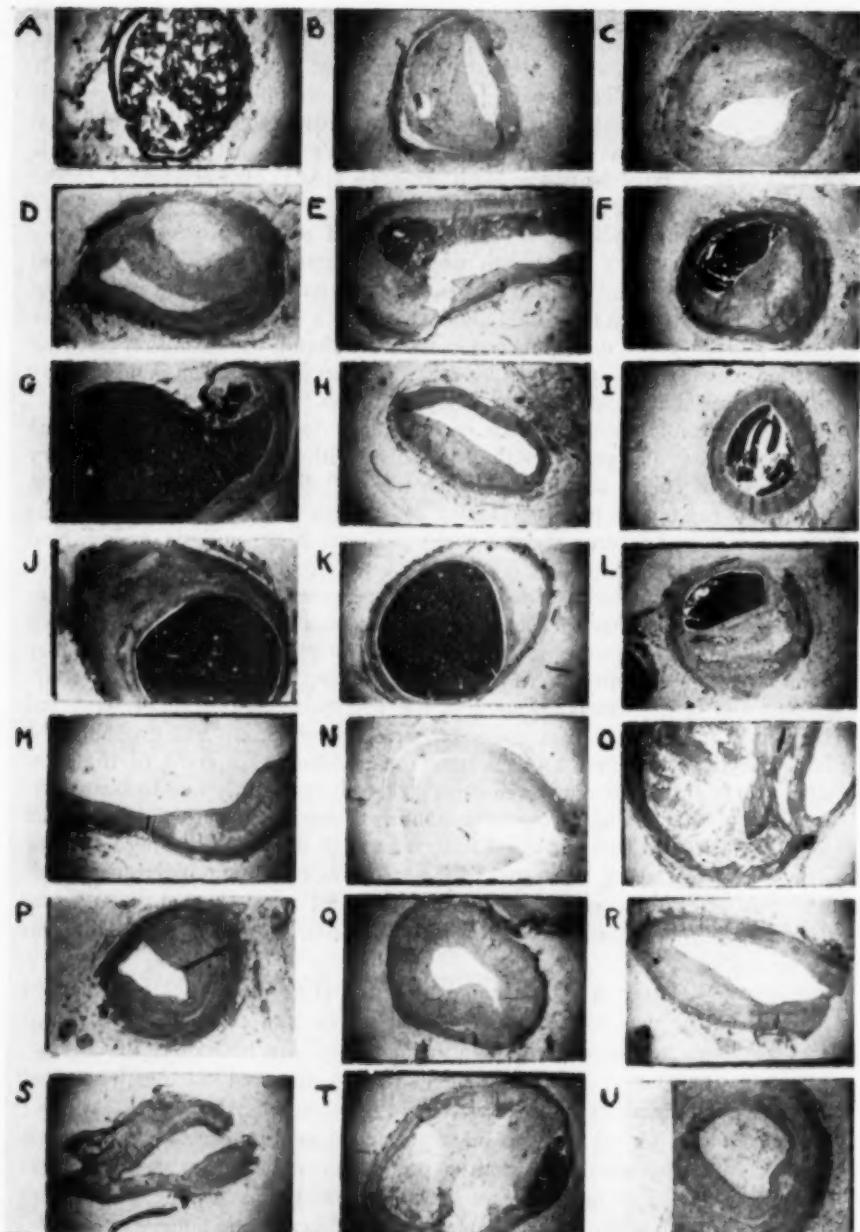


FIG. 3. Photomicrographs of cross-sections of coronary arteries in 21 mesomorphs who died unexpectedly and suddenly from noncardiac cause. There are representations of the maximal area of sclerosis in each individual. The material in the lumen is injection mass.

two hours. She was 5 feet 5 inches in height and weighed 120 pounds. Information obtained from her physician revealed that there was no evidence of diabetes, hypertension or other significant illness. Postmortem examination revealed occlusion of the left anterior descending branch by an atherosclerotic plaque. This plaque extended for a distance of 1 cm. The remainder of this coronary arterial branch, as well as all other branches of the coronary circulation, was, except for occasional streaks, free from atherosclerosis. The aorta had only a slight intimal plaque. The heart weighed 250 gm. (figure 6). A similar case was observed in one of the males in this series. It is of interest that three of the four females with coronary artery disease were dominant mesomorphs.

Two other cases were also of particular interest. These were two prisoners who had complete physical examinations, including electrocardiographic tracings, within one week of death. Medical histories, physical examinations and laboratory procedures at this time were completely negative. Their initial symptoms of coronary artery disease began with precordial pain 25 to 30 minutes prior to death. Postmortem examination revealed advanced coronary atherosclerosis. This of course is a not infrequent happening in medical experience.

TABLE II
Age Distribution of Deaths from Coronary Artery Disease

Age	21-25	26-30	31-35	36-40	41-45
No. of Cases	0	3	9	14	12

Analysis of the character of the activity engaged in just antecedent to the fatal attacks indicates that there is no clear relationship between activity and the onset of these episodes. Analysis of the month of the year and the time of the day during which these episodes occurred also revealed no significant trends. These findings are in agreement with studies of Master and Jaffe,¹² as well as those of Yater and his associates.^{8, 9, 10}

The average estimated body weight for this group was 168 pounds; the average age was 38, and the average heart weight was 415 gm. However, if the two cases with hypertension were eliminated, the average heart weight for the 36 remaining cases was 385 gm. (table 5). Attention is called again to the fact that in many cases complete medical histories were not available. It is therefore possible that, in some of these individuals, signs and symptoms of coronary artery disease may have existed for varying periods of time previous to the terminal episode. However, in all of these subjects, with the exception of the two with hypertension, there was no evidence of arteriolar nephrosclerosis and no cardiac hypertrophy. It would seem reasonable, therefore, that hypertension was not a significant factor. As far as could be determined, there was no history or anatomic evidence of diabetes. Obviously, cholesterol determinations were not available, but

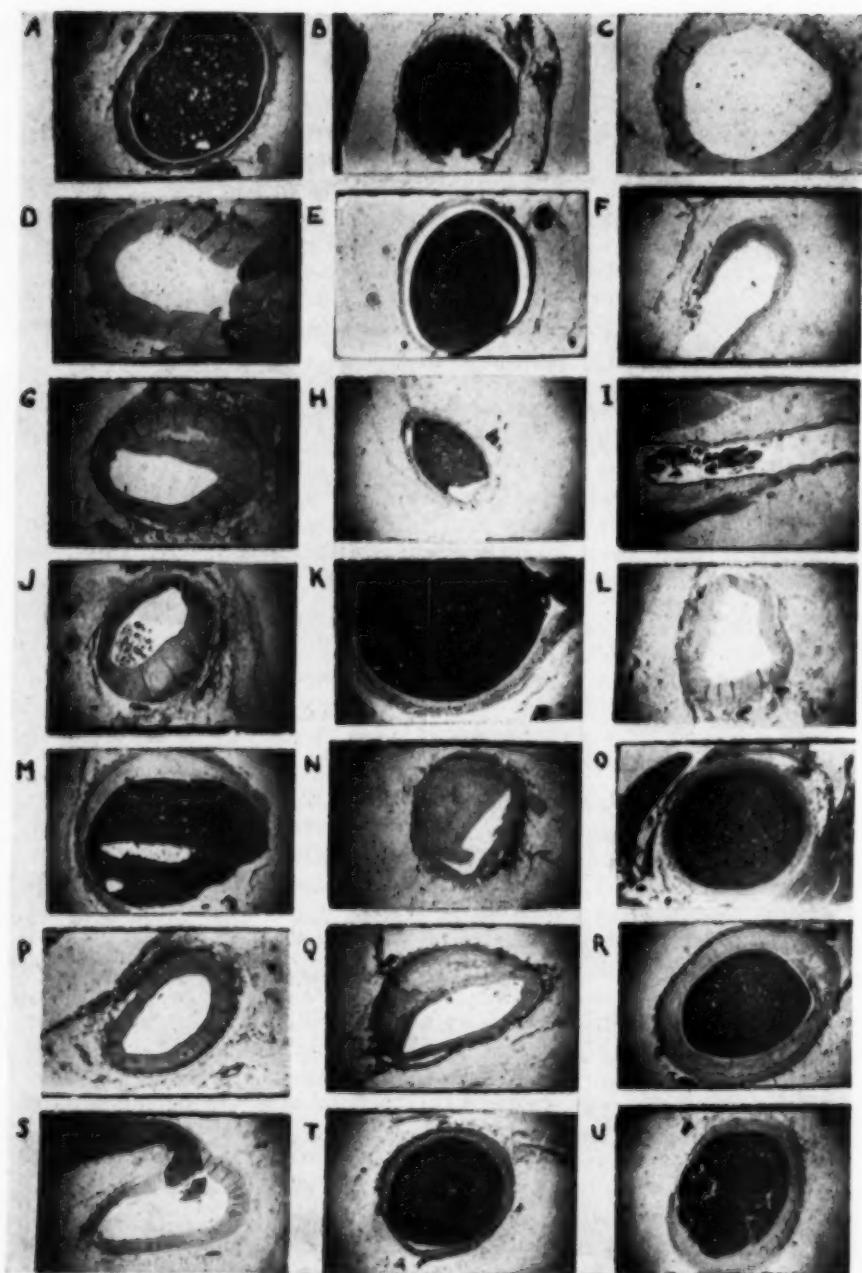


FIG. 4. Photomicrographs of cross-sections of coronary arteries in 21 ectomorphs who died unexpectedly and suddenly from noncardiac cause. There are representations of the maximal area of sclerosis in each individual. The material in the lumen is injection mass.

TABLE III
Degree of Coronary Sclerosis in Noncardiac Deaths
DOMINANT MESOMORPHY

Case	Fig.	Age	Degree of Coronary Sclerosis	Case	Fig.	Age	Degree of Coronary Sclerosis
362A	1A	26	0	601	1K	38	2 plus
145	1B	26	2 plus	568	1L	38	1 plus
490	1C	26	2 plus	124	1M	40	3 plus
931	1D	28	3 plus	905	1N	41	4 plus
385		28	2 plus	933	1O	42	2 plus
532		30	2 plus	736	1P	42	4 plus
769		30	0	533	1Q	44	3 plus
		30	1 plus	66		45	4 plus
814	1E	31	1 plus	920	1R	45	1 plus
864	1F	31	3 plus	552	1S	45	2 plus
656	1G	32	0	555	1T	45	4 plus
520	1H	33	2 plus	664	1U	45	2 plus
556	1I	34	0	668		45	3 plus
-695		36	2 plus	947		45	2 plus
693	1J	36	1 plus				
713		38	1 plus				

DOMINANT ECTOMORPHY

471	2A	20	0	945		37	0
571	2B	20	0	993		38	2 plus
-616	2C	22	0	626	2L	38	1 plus
545	2D	23	1 plus	772	2M	40	2 plus
542	2E	25	0	934	2N	40	0
871	2F	27	2 plus	723	2O	42	0
541	2G	28	0	878	2P	44	2 plus
616	2H	31	0	704	2Q	44	1 plus
940		32	0	624	2R	44	0
549	2I	33	1 plus	566	2S	45	0
-610	2J	35	0	703	2T	45	0
716	2K	36	0	942	2U	45	1 plus

DOMINANT ENDOMORPHY

405		20	0	570		30	1 plus
476		23	0	801		31	0
408		23	0	625		45	1 plus
		30	1 plus				

MIXED

661		19	0	657		34	2 plus
486		20	0	822		37	1 plus
698		25	0	908		40	3 plus
813		28	0	889		43	3 plus
721		29	0	547		43	1 plus
630		32	1 plus	951		45	1 plus

since these cases were consecutive, and since the incidence of familial hypercholesterolemia is supposedly about 5 per cent of the general population, this could not have been an important factor in the group as a whole. The age distribution of these deaths from coronary artery disease is shown in table 4.

TABLE IV
Comparison of Physique with Degree of Coronary Sclerosis in Noncardiac Deaths

Body Type	No. of Cases	Average Age	Degree of Coronary Sclerosis				
			0	1+	2+	3+	4+
Mesomorph	30	36	3	7	10	6	4
Ectomorph	24	35	14	6	4	0	0
Endomorph	7	29	4	3	0	0	0
Mixed	12	33	5	4	1	2	0
Total	73	35	26	20	15	8	4

TABLE V
Comparison of Age, Heart Weight and Body Weight in All Cases

Type	No. of Cases	Average Age	Heart Weight Average (gm.)	Body Weight Average (lbs.)
Coronary Deaths	38 (36)*	38	415 (385)*	168
Noncoronary Deaths				
Mesomorph	30	36	350	163
Ectomorph	24	35	360	152
Endomorph	7	30	370	190
Mixed	12	33	400	169
All Types with No Sclerosis	28	29	370	165

* Number of cases and average weight of hearts after two cases with known hypertension were excluded.

TABLE VI
Degree of Sclerosis at Various Age Levels in All Noncardiac Deaths Under Age of 46

Degree of Sclerosis	Age				
	21-25	26-30	31-35	36-40	41-45
0	10	6	5	3	4
1 plus	1	4	3	5	6
2 plus	0	5	2	4	5
3 plus	0	1	1	2	3
4 plus	0	0	0	0	3
Total	11	16	11	14	21

ANALYSIS OF 73 CONSECUTIVE NECROPSIES ON NONCARDIAC DEATHS

Of the 73 noncardiac deaths in apparently healthy white adult males under 46 years of age, there were 30 mesomorphs, 23 ectomorphs, seven endomorphs and 12 mixed somatotypes. Deaths in these individuals were with few exceptions caused by accident, suicide or homicide. The suicides predominated in the ectomorphs, and death by accident in the mesomorphs. However, these differences were not too striking. Since significant numbers

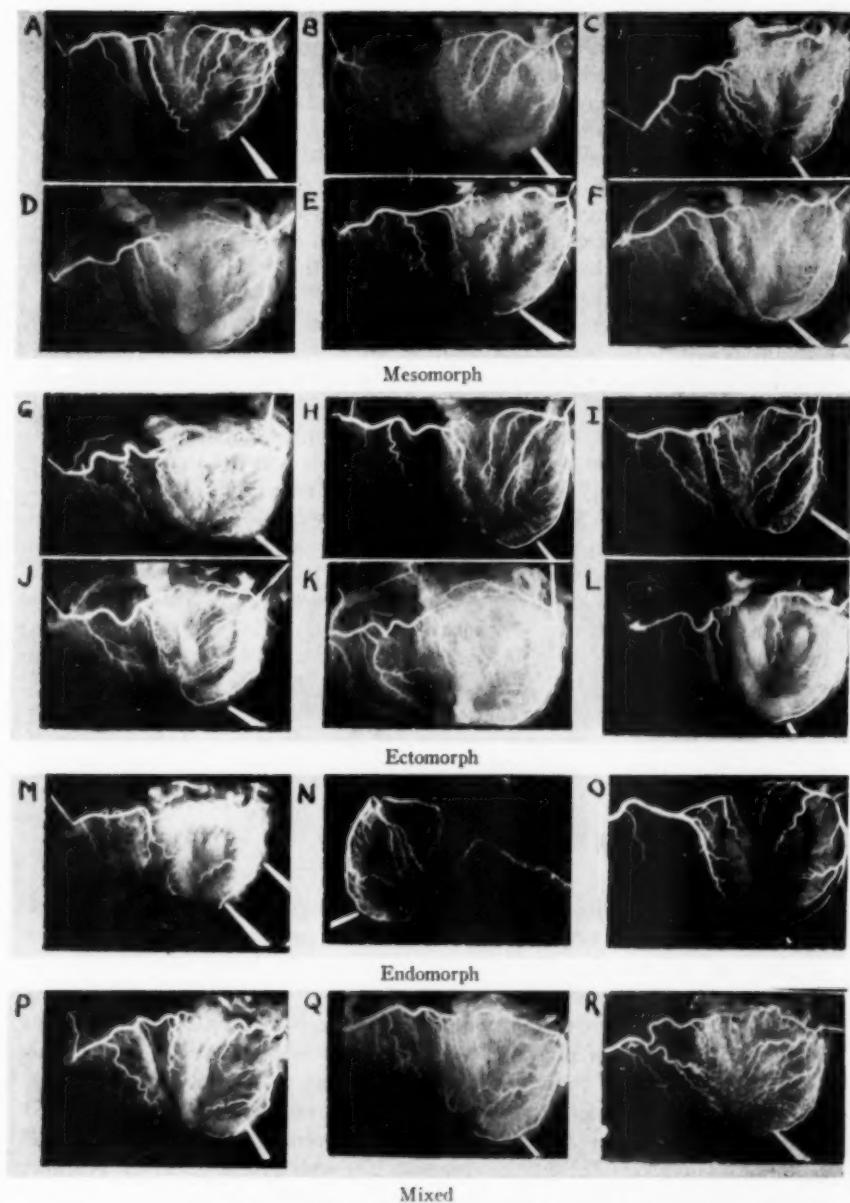


FIG. 5. Photographs of representative roentgenograms of injected coronary arteries in the various somatotypes.

of cases were present only in the mesomorphic and ectomorphic groups, most of the comparisons will be related to these two groups. An analysis of the occupations of the individuals in the various groups indicated that two thirds of the mesomorphs were employed in skilled and unskilled labor, and one third in business, professional-managerial and white-collar positions. This was reversed in the ectomorphic group, where one third were skilled or unskilled laborers and two thirds were in the other classifications. The number in this series belonging to the other somatotypes was too small to warrant detailed consideration. Table 3 shows the age and the degree of coronary sclerosis in the various somatotypes of these individuals who were apparently healthy up to the time of sudden death.

In table 4 the degree of coronary sclerosis is compared in the various somatotypes in these noncardiac deaths. It can be noted that the degree of coronary sclerosis was distinctly more pronounced in the mesomorphs (figures 3 and 4). This was observed to begin in the younger ages and became unquestionably more marked in those approaching the age of 45. The average age of the mesomorphs in this series was 36, that of the ectomorphs, 35. Thus, age as a factor that might account for the differences in the degree of sclerosis in the two somatotypes can be eliminated. In the group of dominant mesomorphs there were 10 cases with 3 plus and 4 plus coronary sclerosis, whereas there was none with such marked sclerosis in the dominant ectomorphs. Of seven endomorphs, not a single case had 3 plus or 4 plus sclerosis. However, the average age in this group was only 29. In the mixed somatype group with an average age of 33, there were two instances out of 12 with 3 plus sclerosis. Atherosclerosis of the coronary arteries was, therefore, most marked in the mesomorphic group, whereas those with a mixed somatype showed a degree of sclerosis between that of the mesomorphic and ectomorphic somatotypes.

ANALYSIS OF HEART WEIGHT, BODY WEIGHT AND PATTERN OF CORONARY CIRCULATION

A study of the heart weight and the body weight in comparison with the degree of coronary sclerosis in both the cardiac and noncardiac death series is presented in table 5. The average weight of the heart was 385 gm. in those dying from coronary artery disease, whereas the average weight was 370 gm. in those cases of the noncardiac series with no atherosclerosis regardless of the type of physique. The differences between the two groups (coronary deaths and those with no sclerosis) as to body weight were also insignificant, the former having an estimated average body weight of 168 pounds and the latter having an estimated average body weight of 165 pounds. The group dying from coronary artery disease was, on the average, 1 inch shorter, but had a greater shoulder width. In only one type of physique, the dominant endomorphs, was there a marked deviation from this

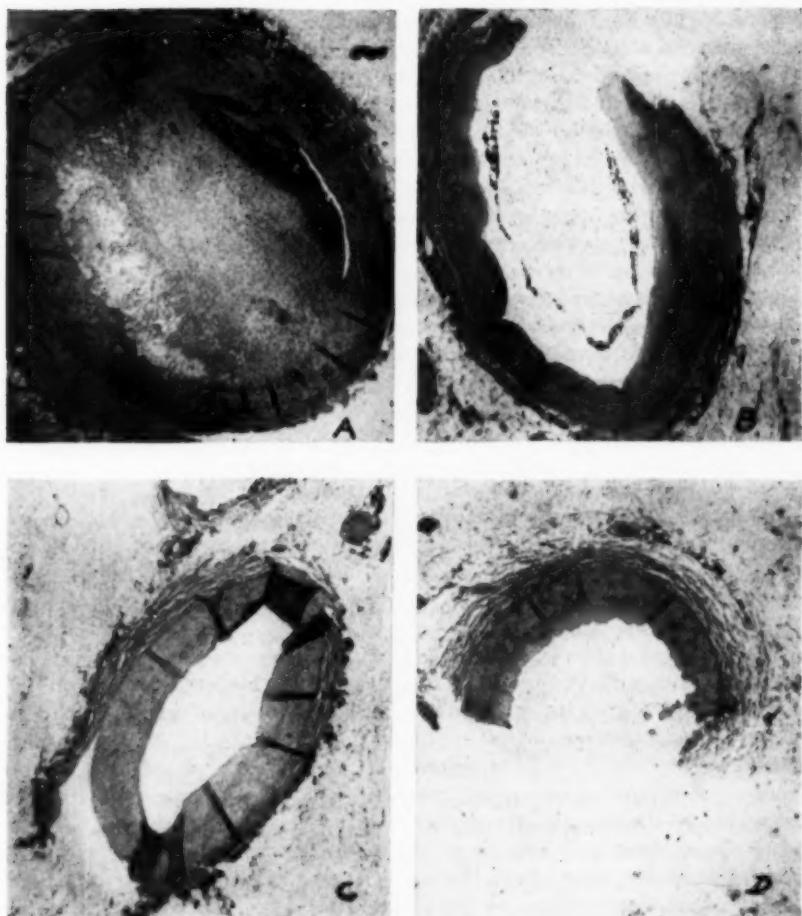


FIG. 6. Photomicrographs of cross-section of coronary arteries in a young female who died suddenly from coronary artery disease. A. Area of maximal involvement with occlusion in left anterior descending branch. This extended for a distance of 1 cm. B. Representative area of maximal involvement in right coronary artery. C. Representative area of maximal involvement in left circumflex branch. D. Representative area of remainder of left anterior descending branch.

estimated average weight. The average weight of the few endomorphs in this study was 190 pounds.

A tabulation of the degree of sclerosis in the various age groups, regardless of physique, is presented in table 6. Of interest is the finding that, in this consecutive series, of those apparently healthy males (between the

ages of 36 and 46), approximately 50 per cent had anatomically significant atherosclerosis of the coronary arteries (2, 3, or 4 plus) (figures 3 and 4).

In 60 of the 111 cases (both cardiac and noncardiac deaths), roentgenograms of the injected coronary arteries were available. These were classified according to the physique of the individual, regardless of the cause of death (figure 5). This was done in an attempt to determine whether any gross differences existed in the general pattern of the coronary tree, in the distribution of the right or left coronary arteries, and in the method of branching. With this admittedly limited method of studying some of these various factors, no difference could be observed among the various somatotypes. All variations existed with equal frequency in all groups. These same roentgenograms were then grouped into two other categories: those individuals who had died from coronary artery disease, and those in the noncardiac series with little or no sclerosis. Again, no difference could be observed.

DISCUSSION

It is quite evident, at least in this study, that atherosclerosis of the coronary arteries is more pronounced and develops at an earlier age in the mesomorphic individuals than in those of the other somatotypes. Perhaps an advance in the understanding of the pathogenesis of this process would result if the reason or reasons for this difference in the rate of development of coronary atherosclerosis were known. Several basic possibilities have been considered. The question of inherent, developmental or acquired biochemical differences in these somatotypes has been under investigation.^{17, 18} Another basic difference might exist in the anatomic structure or pattern of the coronary arteries. Finally, the variations might be of a more subtle nature, in that the pattern of behavior of the mesomorph, at least in this culture or in this particular environment, might be significantly different from that of the other somatotypes. Gertler and his associates⁵ have recently listed a group of criteria to aid in the possible prediction of the development of coronary artery disease in young individuals. Among these criteria was the somatotype of the individual. They believe that the dominant mesomorph with secondary characteristics of endomorphy is the individual most likely to develop coronary atherosclerosis. Tanner¹⁹ in a very carefully controlled study, has indicated that cholesterol levels may be correlated with the endomorphic component of physique. Stamler,²⁰ in studies on the experimental production of atherosclerosis in chickens, has found that the variations in estrogen levels may alter the rate of deposition of lipid in the arterial walls. Investigations as to whether estrogen levels differ among the various somatotypes are therefore probably indicated. In all such studies, however, caution must be exercised that associated findings are not mistaken for a definite cause-and-effect relationship. This of course raises the entire question of the relative importance of disturbances in the various phases of cholesterol metabolism in the development of atheroscle-

rosis. Such observers as Gofman,² Morrison³ and others believe that this relationship is of major importance. However, Wilkinson and others^{21, 22} have failed to demonstrate any such clear relationship. Furthermore, Keys,⁴ in an analysis of the methods used by some of these investigators, has concluded that there is no proof to date that either the determination of concentrations of "giant molecules" or the estimation of cholesterol-phospholipid ratios has any advantage over the other in distinguishing between individuals with coronary artery disease and those without, nor is there any apparent advantage of one of these determinations over any of the others in predicting the development of coronary artery disease. The evidence to date is based upon studies in which these determinations in individuals with known coronary artery disease are compared with those in a similar group of supposedly healthy controls. Results of our study indicate that many of the individuals who were regarded as healthy up to the time of sudden violent death had quite extensive atherosclerosis of the coronary arteries. They were symptom-free, and it is most likely that, even if ballistocardiographic studies and exercise tolerance tests had been performed, some of them would still have been considered free of coronary arterial or cardiac disease. (Studies with the procedures above mentioned indicate a considerable error even in those with typical angina.²³) In any study, therefore, these might have been numbered among the controls. Schlesinger has shown that an individual with a coronary circulation in which the left coronary artery predominates would more readily have signs and symptoms of coronary insufficiency when this vessel is involved than would an individual with the same or an even greater degree of atherosclerosis in whom the right coronary artery predominates. Since there is no available clinical method for determining the pattern of the coronary circulation, this would tend to obscure further the selection of proper controls.

In many instances there is only a moderate degree of coronary atherosclerosis with superimposed thrombi as the underlying mechanism in the production of coronary insufficiency. It is this superimposed thrombus which produces the clinical picture. Nevertheless, there are numerous individuals with diffuse atherosclerosis of the coronary arteries in whom there is no significant obstruction to the flow of blood. In these individuals, although quantitatively a greater degree of cholesterol has been deposited in the coronary walls, there often are no physical signs and symptoms of coronary artery disease. Because of local vascular factors in some, an advanced degree of atherosclerosis may be localized at one strategic point in the coronary circulation. This, again, would produce a clinical picture out of proportion to the amount of cholesterol deposited. The entire problem of the selection of controls upon which the ultimate significance of the observations of Gofman and others is dependent should lead to caution in the formulation of any conclusions. Although Gofman²⁴ is aware of these pitfalls, the tendency has been to underestimate their importance in arriving at

valid conclusions. Many of the studies concerning the various aspects of cholesterol metabolism as related to the development of coronary artery disease have been based upon one or two determinations taken during the life of the particular individual being studied. This determination has been compared or related to the individual's clinical status at that particular time. Of more significance are the reports of Morrison,^{25, 26} in the most recent of which serum phospholipid/cholesterol determinations were performed on five alternate days in two groups of individuals (a group with coronary artery disease and a group of apparently healthy controls). This study indicated that greater fluctuations of cholesterol levels existed from day to day in the coronary disease group than in the average of the control group as a whole. Perhaps the most significant study of all has not yet been done, or at least completed, i.e., serial determinations of the various aspects of serum lipids over a period of many years in a large group of individuals, beginning in early adult life. Changing levels that might take place in these subjects could then be correlated with the development or nondevelopment of coronary artery disease.

The findings of spontaneous atherosclerosis of the coronary arteries in dogs with little or no lipid in the lesions,²⁷ the production of lipid-free arteriosclerosis in the coronary arteries of monkeys on pyridoxine deficient diets,²⁸ the results of the study on atherosclerosis using histochemical and fluorescent microscopic methods by Joel and Hopps,²⁹ the lipid-free changes that occur in blood vessels following operative stress and conditions of shock,³⁰ the development of hyaline sclerosis in the small pulmonary vessels³¹ and the development of phlebosclerosis³² in the absence of demonstrable lipid in the walls of these vessels, the lipid-free changes that occur in the aorta and coronary arteries of infants and young children,³³ and the experimental production in dogs of vascular injury following short episodes of epinephrine-induced hypertension,³⁴ all indicate that it is possible for arteriosclerosis of the coronary arteries to develop independently of and prior to the deposition of lipid in these lesions.

Even without referring to any of the extensive experimental evidence of production of atherosclerosis in animals, there is no doubt that cholesterol is a factor of varying importance in the entire picture; one need only note the development of atherosclerosis in such conditions as diabetes mellitus, familial hypercholesterolemia, nephrosis and myxedema. Nevertheless, this does not explain entirely the main problem as seen in the over-all picture of coronary atherosclerosis and, in particular, of those instances of its development in younger individuals in the absence of the aforementioned conditions. The exact place and importance of altered lipid metabolism in the dynamic complex of constitutional background, local vascular factors and environmental stress and the cortical-visceral pathway through which this may be mediated are as yet not clear.

The possibility must be considered that anatomic differences in the configuration, angles of branching and points of fixation of the coronary arteries might account for the difference in the degree of atherosclerosis among the various somatotypes. Schlesinger⁷ has demonstrated that several different coronary patterns exist. In 48 per cent the right coronary artery predominated, in 18 per cent the left coronary artery predominated, and in 34 per cent the circulation was shared equally by both major branches. Those with a predominating left coronary circulation suffer the worst consequences of coronary atherosclerosis. Occasionally, a marked disproportion between the right and left coronary arteries has been the basis for the development of extensive atherosclerosis of the coronary arteries in young individuals. Dock³⁵ has claimed that the intimas of the coronary arteries of males were thicker than those of females. However, this finding has not been substantiated, and there is no evidence of intimal differences among the various somatotypes. The findings in this study based on roentgenograms of injected coronary arteries do not support the view that anatomic differences of the coronary arterial tree among the various somatotypes are the basis for the earlier development of a greater amount of atherosclerosis in the mesomorphic male. There is, however, a need for further study of local physical factors. Acquired anatomic alterations on the basis of inflammatory disease such as rheumatic fever may at times account for the early development of advanced atherosclerosis of the coronary arteries in young individuals. In only one necropsy in this group was it possible to identify what may have been an underlying inflammatory lesion in the coronary arteries. Atherosclerosis itself may produce inflammatory reactions in the coronary artery that must be carefully distinguished from those considered to be primarily inflammatory in origin.

Many mesomorphs in this culture may follow for various reasons a pattern of behavior quantitatively different from that of the other somatotypes.¹¹ Because of our great interest in athletics and feats of skill and daring, those who happen to have the best muscular coördination and development would, for prestige and other reasons, be the ones most likely to be involved in these types of activity. These activities are associated not only with sudden episodes of physical stress, but also, of necessity, because of their violence and daring, with greater degrees of emotional stress. These events may temporarily increase the tension and the flow of blood through the coronary arteries, with the resultant strain on these vessels and a temporary increase in filtration pressure favorable to the passage of lipid into the arterial walls. Wolf³⁶ has shown that there is a wide variety of circulatory responses to life situations which affect not only the heart rate but the blood pressure, stroke volume and blood viscosity as well.

Yater's interesting observation that twice as many young individuals who had coronary artery disease walked before the age of 17 months as in a comparable group of normal controls; the finding of Gertler and of this

study regarding the earlier development of coronary atherosclerosis in mesomorphs; the greater incidence of the process in young males as compared to young females; the significantly more frequent incidence in general practitioners of medicine than in consultants or specialists as reported in England, and the higher rate in the older than in the younger individuals, all have a common denominator. This common denominator might be regarded as being quantitatively and qualitatively a greater exposure to stressful situations. It would surely be a peculiar type of chemical defect that would be selective as far as this group of situations is concerned. Relative to this, it has recently been observed that cortisone, a hormonal product of stress, may be one of the factors involved in the development of the process. An investigation by Etheridge and Hoch-Ligeti³⁷ of the degree of lipid deposition in the aortas of children who had been treated with cortisone and adrenocorticotropic hormone revealed larger deposits of lipid in both the intima and media than in a comparable group that had not received these hormones. It is also known that cortisone, through mechanisms as yet incompletely understood, may also alter serum cholesterol levels.³⁸ This may be an important step in the entire process. Related to this is the experimental evidence that the atherosclerosis most likely develops in an episodic manner rather than as a gradual continuous process.³⁹

Some investigations in which attempts have been made to correlate occupation with coronary artery disease have been superficially approached. Usually in these studies no information was available regarding the method of the individual performance in the particular occupation, or of the individual's extra-occupational activities. Thus a mesomorph might occupy a sedentary white-collar position but also have a long history of athletic activity. A mine worker might perform his duties in a steady, regulated manner and relax in off-hours. On the other hand, a clerical worker might work under tension to meet a dead-line. Any concept of the development of coronary artery disease must not only be sufficiently dynamic to explain the development of atherosclerosis in the young mesomorphic athlete, but must also account for the appearance of coronary atherosclerosis in the 33 year old ectomorphic fighter-plane pilot of World War II who had spent one year in a German prison camp. It is possible in such a case (one of the 38 cardiac deaths in this study) that not only the physical but also the emotional stresses associated with his activities as a pilot and with time spent in a German prison camp could have played an important part in the early development of advanced coronary atherosclerosis which resulted in death. Before it is possible to arrive at any conclusions that mesomorphs as such, because of something inherent in their constitutions, are more predisposed toward the development of coronary atherosclerosis, comparable anatomic and biochemical studies in relation to these somatotypes and to the degree of coronary atherosclerosis present in them must be determined in forms of culture other than our own.

It is difficult to reconcile some of the claims⁴⁰ regarding the relationship of obesity (and hence diet) to the development of coronary atherosclerosis, with the repeated observations in this study of advanced coronary atherosclerosis in lean, well muscled individuals. Many others have also failed to find any increase in weight over the normal controls in those with coronary artery disease in the younger age groups. It is possible, however, that obesity may be related to the development of coronary artery disease in the older age groups as a result of altered cholesterol metabolism. It is also possible that the extra work of the heart necessitated by increased adipose tissue may bring to the fore a clinically latent coronary insufficiency. Perhaps the relative rate of weight gain or weight loss is more important than the weight of the individual at any one time. There is some experimental and clinical evidence to support this latter view.^{41, 42}

The effect of coronary insufficiency on the size of the heart has been a subject of discussion for some time. In this study, as well as in others, there was no significant difference in heart size between the group with normal coronary arteries and those with advanced coronary atherosclerosis. It is possible that the somewhat larger hearts seen in the older individuals with coronary artery disease may be related to extra work associated with congestive failure rather than to ischemia secondary to coronary occlusion.

SUMMARY

1. The degree of coronary atherosclerosis was studied in 111 consecutive necropsies in white males under the age of 46. Thirty-eight of these died suddenly and unexpectedly from coronary artery disease, while the remaining 73 died suddenly from sudden, unexpected, violent death.
2. Of the 38 consecutive deaths from coronary artery disease, 24 were dominant mesomorphs, three were dominant ectomorphs, three were dominant endomorphs and eight were a mixed somatotype.
3. No significant relationships were noted between those with coronary artery disease and their occupation, or their ethnic groups.
4. The major anatomic finding in these deaths from coronary artery disease was simple sclerotic narrowing with varying degrees of obstruction. Unusual findings were thrombi or myocardial infarcts.
5. Inflammation of the coronary arteries as a basis for the later development of sclerosis was encountered only once.
6. No significant relationship was noted between the onset of the fatal attack and activity just prior to this, nor was there any correlation to the time of the day or season of the year.
7. In the 73 apparently healthy white males under the age of 46 who died from violent means, the degree of atherosclerosis of the coronary arteries was definitely greater in the dominant mesomorphs than in the dominant ectomorphs.

8. One-half of these apparently healthy young males between the ages of 36 and 46 had anatomically significant coronary atherosclerosis. The bearing of this on the question of normal controls in clinical studies on cholesterol has been commented on.

9. No relationship was noted between obesity and coronary atherosclerosis.

10. There were no differences in heart weight in those with coronary artery disease as compared with those with relatively uninvolved coronary arteries.

11. No anatomic differences in the pattern of the coronary circulation were noted among the various somatotypes, nor were any noted between those with and those without coronary artery disease.

BIBLIOGRAPHY

1. Kellner, A.: Lipid metabolism and atherosclerosis, *Bull. New York Acad. Med.* **28**: 11, 1952.
2. Gofman, J. W.: The role of lipids and lipoproteins in atherosclerosis, *Science* **111**: 166, 1950.
3. Morrison, L. M., and Gonzales, W. F.: Results of treatment of coronary arteriosclerosis with choline, *Am. Heart J.* **39**: 729, 1950.
4. Keys, A.: Cholesterol, "giant molecules" and atherosclerosis, *J. A. M. A.* **147**: 1514, 1951.
5. Gertler, M. M., Garn, S. M., and White, P. D.: Young candidates for coronary heart disease, *J. A. M. A.* **147**: 621, 1951.
6. Sheldon, W. H.: The varieties of human physique, 1940, Harper and Bros., New York.
7. Schlesinger, M. J.: An injection plus dissection study of coronary artery occlusions and anastomoses, *Am. Heart J.* **15**: 528, 1938.
8. Yater, W. M., Traum, A. H., Brown, W. G., Fitzgerald, R. P., Geisler, M. A., and Wilcox, B. B.: Coronary artery disease in men eighteen to thirty-nine years of age. Part I, *Am. Heart J.* **36**: 334, 1948.
9. Yater, W. M., Traum, A. H., Brown, W. G., Fitzgerald, R. P., Geisler, M. A., and Wilcox, B. B.: Coronary artery disease in men eighteen to thirty-nine years of age. Part II, *Am. Heart J.* **36**: 481, 1948.
10. Yater, W. M., Traum, A. H., Brown, W. G., Fitzgerald, R. P., Geisler, M. A., and Wilcox, B. B.: Coronary artery disease in men eighteen to thirty-nine years of age. Part III, *Am. Heart J.* **36**: 683, 1948.
11. Sheldon, W. H.: The varieties of temperament—a psychology of constitutional differences, 1942, Harper and Bros., New York.
12. Gertler, M. M., Driskell, M. M., Bland, E. F., Garn, S. M., Lerman, J., Levine, S. A., Sprague, H. B., and White, P. D.: Clinical aspects of coronary heart disease, *J. A. M. A.* **146**: 1291, 1951.
13. Master, A. M., and Jaffe, H. L.: Factors in the onset of coronary occlusion and coronary insufficiency, *J. A. M. A.* **148**: 794, 1952.
14. Morris, J. N., and Heady, J. A.: Coronary heart disease in medical practitioners, *Brit. M. J.* **1**: 503, 1952.
15. Saphir, O., and Gore, H.: Evidence for an inflammatory basis for coronary arteriosclerosis in the young, *Arch. Path.* **49**: 418, 1950.
16. Adlersberg, D., and Zak, F. G.: Atherosclerosis of early age: clinical and pathological study, *Circulation* **2**: 473, 1950.
17. Gertler, M. M., Garn, S. M., and Lerman, J.: Interrelationship of serum cholesterol, cholesterol esters and phospholipids in health and in coronary artery disease, *Circulation* **2**: 205, 1950.

18. Garn, S. M., Gertler, M. M., Levine, S. A., and White, P. D.: Body weight versus weight standards in coronary artery disease and a healthy group, *Ann. Int. Med.* **34**: 1416, 1951.
19. Tanner, J. M.: The relation between serum cholesterol and physique in healthy young men, *J. Physiol.* **115**: 371, 1951.
20. Stamler, J.: Presented before Council for High Blood Pressure Research of American Heart Association, 1952.
21. Wilkinson, C. F., Blecha, E., and Reimer, A.: The relationship between dietary composition and the blood cholesterol level, *Am. Heart J.* **36**: 472, 1948.
22. Goldblum, A. A., and Pomeranz, J.: Blood lipid studies in cardiovascular disease, presented at Annual Meeting of New York State Medical Society, 1952.
23. Pordy, L., Master, A. M., and Chesky, K.: Value of cardiac function tests in industry, *J. A. M. A.* **148**: 813, 1952.
24. Gofman, J. W.: Diet and lipotropic agents in atherosclerosis, *Bull. New York Acad. Med.* **28**: 279, 1952.
25. Morrison, L. M.: The serum phospholipid-cholesterol ratio as a test for coronary atherosclerosis, *J. Lab. and Clin. Med.* **39**: 550, 1952.
26. Morrison, L. M., Gonzales, W. T., and Hall, L.: The significance of cholesterol variations in human blood serum, *J. Lab. and Clin. Med.* **34**: 1473, 1949.
27. Lindsay, S., Chaikoff, I. L., and Gilmore, J. W.: Arteriosclerosis in the dog. I. Spontaneous lesions in the aorta and the coronary arteries, *Arch. Path.* **53**: 281, 1952.
28. Rinehart, J. F., and Greenberg, L. D.: Arteriosclerotic lesions in pyridoxine deficient monkeys, *Am. J. Path.* **25**: 481, 1949.
29. Joel, W., and Hopps, H. C.: Atherosclerosis using histochemical and fluorescent microscopic methods, *Federation Proc.* **11**: 418, 1952.
30. Pollack, O. J.: An etiologic concept of atherosclerosis based on study of intimal alterations after shock, *Circulation* **5**: 539, 1952.
31. Spain, D. M., and Rosenschein, J.: The absence of lipid in pulmonary arteriolarsclerosis, presented at Annual Meeting of Am. Assoc. Path. and Bact., 1952.
32. Lev, M., and Saphir, O.: Endophlebo-hypertrophy and phlebosclerosis, *Am. J. Path.* **26**: 727, 1950.
33. Lev, M., and Sullivan, C. M.: The relationship of aging changes to the development of arteriosclerosis in the human aorta, *Am. J. Path.* **27**: 684, 1951.
34. Waters, L. L.: Changes in the coronary and visceral arterioles of dogs following large doses of adrenalin, *Am. J. Path.* **26**: 697, 1950.
35. Dock, W.: Predilection of atherosclerosis for the coronary arteries, *J. A. M. A.* **131**: 875, 1946.
36. Wolf, S.: Circulatory responses to life situations, *Bull. New York Acad. Med.* **28**: 168, 1952.
37. Etheridge, E. M., and Hoch-Ligeti, C.: Lipid deposition in aortas in younger age groups following cortisone and adrenocorticotropic hormone, *Am. J. Path.* **27**: 315, 1952.
38. Kyle, L. H., Hess, W. C., and Walsh, W. P.: The effect of ACTH, cortisone, and operative stress upon blood cholesterol levels, *J. Lab. and Clin. Med.* **39**: 605, 1952.
39. Holman, R. L.: Does arteriosclerosis develop by episodic stages? *Am. Heart J.* **38**: 469, 1949.
40. Gofman, J. W., and Jones, H. B.: Obesity, fat metabolism and cardiovascular disease, *Circulation* **5**: 514, 1952.
41. Firstbrook, J. B.: The effect of changes in body weight on atherosclerosis in the rabbit, *Science* **111**: 31, 1950.
42. Wilens, S. L.: Bearing of general nutritional state on atherosclerosis, *Arch. Int. Med.* **79**: 129, 1947.

CHRONIC ANTICOAGULANT THERAPY IN RECURRENT EMBOLISM OF CARDIAC ORIGIN *

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MAJOR arterial occlusions by emboli constitute one of the serious complications encountered in patients with chronic cardiac disease, particularly in individuals with inactive rheumatic mitral stenosis. Clinically recognizable embolism occurs in from 4 to 8 per cent of patients with chronic rheumatic heart disease,^{1, 2} and 60 per cent of these experience multiple episodes of vascular occlusion. In individuals with multiple embolism 75 per cent of the recurrences take place within one year of the initial episode.³

Mural thrombus formations in one or more chambers are found in between 13 and 56 per cent of the autopsy examinations of patients with mitral stenosis.^{4, 5, 6} The occurrence of these mural thrombi appears to be increased particularly by auricular fibrillation, as well as by the advancing age of the patient.⁷ Once a patient has experienced one or more embolic episodes, it is logical to consider seriously the institution of prophylactic measures aimed at reduction of further intracardiac thrombus formation as a means of decreasing the frequency of future recurrent embolism.

During the past five years an ambulatory anticoagulant program has been under study at the Presbyterian Hospital. As part of this program, 28 patients with recent embolic complications of cardiac origin have been treated continuously with Dicumarol for periods up to as long as 56 months. It is the purpose of this present report to summarize this experience.

ANTICOAGULANT THERAPY

Dicumarol was the principal anticoagulant employed in this program, heparin being used only in certain cases during the immediate period of one to four days after the acute embolism. During the initial two to three weeks' period of stabilization of an individual's reaction to Dicumarol, the patient was usually hospitalized and prothrombin time determinations were obtained daily. In the third to sixth weeks, prothrombin times were performed every two or three days on an out-patient basis. Once the maintenance dose of Dicumarol was determined, it was possible to obtain satisfactory control by a prothrombin time test done once weekly. Exceptions have included a physician-patient who was allowed to have a prothrombin time at monthly intervals, due to his extraordinarily steady reaction to Dicumarol, and occasional patients who took summer vacations and were checked only at two to three week intervals. However, variations in an individual's response to

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a given schedule have been observed frequently enough to make a weekly test more desirable.

Dicumarol was given in dosage of 300 mg. on Day 1 and 200 mg. on Day 2. The average daily maintenance dose was between 50 and 100 mg. In a few patients Dicumarol was omitted on one or occasionally two days a week. The program was carried out in the belief that employing a moderate daily ration of anticoagulant was preferable to a regimen employing intermittent massive doses.

The prothrombin time was performed on whole plasma according to a modification of Quick's one-stage technic.⁸ The normal value for this technic, using a commercially supplied rabbit lung thromboplastin, was between 14 and 15 seconds. Needless to say, a carefully performed and reliable prothrombin time test is an absolute necessity for safety and successful therapy. The "therapeutic range" of the prothrombin time employed in the study was 22 to 40 seconds. With this laboratory's control prothrombin times of 14 to 15 seconds, these values are related respectively to values of 30 per cent and 15 per cent of normal prothrombin activity. This is the same therapeutic range employed at this institution in patients who are hospitalized during their entire anticoagulant course for such conditions as cardiac infarction or venous thromboembolic disease. The prothrombin time was generally maintained in this therapeutic range, although there were observed not infrequently the unexplained excessive up and down swings of prothrombin time from week to week in the same individual on the same dosage of Dicumarol. In particular, great caution was exercised to reduce to a minimum the incidence of excessive hypoprothrombinemia (i.e., prothrombin time above 40 seconds), since approximately 85 per cent of the more serious hemorrhagic complications observed on this service during the past several years have been correlated with periods in which the prothrombin time was in excess of 40 seconds. Furthermore, it is generally agreed that no additional benefit occurs when the prothrombin time is above 40 seconds. Nevertheless, excessive hypoprothrombinemia did occur from time to time despite this care in estimating Dicumarol dosage. On such occasions, water-soluble vitamin K (menadione bisulfite) or fat-soluble vitamin K₁ was administered to those patients who had incurred a potentially dangerous elevation of the prothrombin time.

One severe hemorrhagic episode occurred in this treatment group. The patient experienced a major upper gastrointestinal hemorrhage at a period when the prothrombin time had been unintentionally elevated to 49 seconds as a result of a mistake in dosage. The hypoprothrombinemia responded promptly to the intravenous administration of 50 mg. of vitamin K₁ and it was not necessary to resort to transfusion. In two patients, menstrual bleeding seemed to be increased during the time of anticoagulation. Gross hematuria was seen in one patient, moderate expistaxis in two individuals. Positive stool guaiacs without gross bleeding or tarry consistency of the

stools were encountered in several patients, but were not interpreted as a contraindication to the cautious continuation of Dicumarol. An increased ease of bruising was noted in a few individuals during therapy.

CLINICAL MATERIAL

Twenty-eight patients were studied. As several subjects in this group had received a first course of anticoagulation for a period of months, followed by cessation of treatment and later reinstitution of anticoagulant therapy, a total of 35 "patient-courses" have been observed. There were 19 female and nine male patients, and 19 of the total series were in the third and fourth decades.

Twenty-six of the 28 patients were considered to have chronic rheumatic valvular disease with mitral stenosis or combined stenosis and insufficiency of the mitral valve; aortic insufficiency was also present in two instances. The remaining two patients had chronic constrictive pericarditis and auricular fibrillation.

Auricular fibrillation was present in 27 of the 28 patients. In a majority the arrhythmia had been present for more than one year.

EMBOLI

Among these 35 "patient-courses" 103 embolic episodes had occurred prior to the start of anticoagulant therapy (table 1). These 103 embolic episodes had occurred over a period of 275 "patient-months" prior to the institution of anticoagulation. Embolic occlusions of the systemic arteries were more numerous than those of the pulmonary arterial circulation, 77 per cent of the emboli apparently originating from the left side of the heart. Ten of the 28 subjects gave evidence of embolism to both systemic and pulmonary circuits. The majority (71 per cent) of these episodes had taken place within six months of each other, while the remainder had occurred over a period of 11 to 48 months.

In only four instances had there been but one embolism before the initiation of therapy. In 13 of the "patient-courses" two emboli had been experienced; in 14 instances, three to five emboli had occurred, and in three of the "patient-courses" there had occurred nine, 11 and 13 embolic episodes before Dicumarol treatment. The serious nature of such arterial occlusions was indicated by the fact that two patients had become hemiplegic, two other patients had undergone amputation of a lower extremity, and one individual had been experiencing severe incapacitating claudication of both lower extremities following bilateral emboli to the legs.

RESULTS

As stated above, the 28 patients in this series have been considered as 35 "patient-courses." The clinical data pertaining to the number of emboli

prior to anticoagulation, duration of therapy and emboli occurring during anticoagulation are presented in table 1.

Embolus During Treatment: Thirteen embolic episodes have occurred in eight patients during anticoagulant therapy. Four of these took place within

TABLE I
Chronic Anticoagulant Therapy in Recurrent Embolism of Intracardiac Origin

Patient	Embolus Before Therapy	Duration of Anticoagulant Therapy (Months)	Embolus During Therapy
1. M. H.—I	1	6	0
2. M. H.—II	1 + 1†	10	0
3. C. P.	4	4	0
4. A. A.—I	3	9	0
5. A. A.—II	3 + 1	20*	2
6. C. P.—I	3	6	0
7. C. P.—II	3 + 2	6	0
8. B. B.	2	11	0
9. C. F.	1	3	0
10. F. F.	1	6	0
11. P. D.	2	4	0
12. A. E.	2	5	0
13. A. M.—I	2	12	0
14. A. M.—II	2 + 1	24	0
15. A. M.—III	2 + 1 + 1	20*	0
16. E. O.—I	2	19	0
17. E. O.—II	2 + 1	16	4
18. M. K.	2	13	0
19. F. Y.	4	18	0
20. A. G.	3	30*	2†
21. A. F.	2	32*	0
22. F. G.	4	12*	0
23. L. M.	1	11	0
24. H. H.	2	44*	0
25. P. L.	9	56*	1
26. R. C.	2	12	0
27. M. T.	6	46*	0
28. B. L.	11	55*	0
29. A. S.—I	2	15	1
30. A. S.—II	2 + 1	38*	0
31. W. H.	13	28	1
32. M. C.	3	19*	1†
33. J. F.	2	1.5	0
34. S. E.	2	1.5	1†
35. J. A.	4	12	0
Total: 35	103	625	13

* Currently under treatment (May 23, 1952).

† Embolus occurred within six weeks of start of anticoagulation.

‡ Under the "emboli before therapy," the numbers with a plus (e.g., 3 + 1) refer to the number of emboli occurring before separate courses of therapy, e.g. 3 + 1 indicating that the first course was preceded by 3 emboli and the second by 1 embolus.

Roman numerals (I, II or III) in column 1 refer to the first, second or third separate courses of anticoagulant therapy to the same patient.

six weeks of the start of treatment. Patient 32 experienced a splenic embolus five days after the start of anticoagulants, but has since been treated uneventfully for 13 months. Patient 20 experienced two emboli on the fifteenth and thirty-fifth days of anticoagulation, but received subsequent therapy un-

eventfully for 24 months. Patient 34 developed a saddle embolism of the aorta six weeks after initiation of therapy, which was successfully treated with aortic embolectomy and later auricular appendectomy. In this subject anticoagulant therapy had been inadequately conducted, since the prothrombin time had been allowed to remain below the therapeutic range for three weeks prior to the day when the embolism occurred.

Two other embolic episodes were questionable. Patient 5 complained of unexplained abdominal pain for three days in her ninth month of treatment; patient 29 experienced costovertebral angle pain without other signs of embolism in her fourth month of Dicumarol.

TABLE II
Occurrence of Embolism after Cessation of Chronic Anticoagulant Therapy

Patient	Duration of Therapy (Months)	Embolism After Therapy Stopped	Interval from Cessation of Therapy to Embolism	Total Follow-Up Period After Cessation of Therapy (Months)
1. C. P.	4	0	—	11
2. F. F.	6	0	—	41
3. P. D.	4	0	—	36
4. F. Y.	18	0	—	20
5. R. C.	12	0	—	31
6. A. M.—II	24	1—Cerebral	2 days	2 days
7. E. O.—I	19	1—Spleen	3 days	3 days
8. J. F.	1½	1—Cerebral	5 days	18
9. B. B.	11	1—Cerebral	11 days	11 days
10. C. P.	6	2—Cerebral Cerebral	2 weeks 10 months	11
11. C. F.	3	2—? Lung Lung	2 weeks 4 weeks	1
12. A. M.—I	12	1—Pulmonary	3 weeks	1
13. A. S.—I	15	1—L. Leg	2½ months	3
14. A. A.—I	9	1—L. Femoral	4 months	4
15. M. K.	13	1—R. Leg	10 months	31
16. M. H.—I	6	1—L. Popliteal	23 months	23
17. M. H.—II	10	1—? Pulmonary	2 months	7

Patient 16 was treated uneventfully for 19 months, at which time therapy was stopped because she had done so well during that period and her physician was undecided as to whether the anticoagulation was of significant benefit. Three days after the prothrombin time had returned to normal range she experienced a splenic infarct. Her second course of anticoagulants was then started (as patient 17). Between the seventh and twelfth months after the resumption of this second course of therapy she experienced four emboli (renal, cerebral, renal and pulmonary). It is believed that these latter four emboli were related to mural thrombi which may have been permitted to be formed in the auricular chambers during the few days between her first and second anticoagulant courses, and which might have been avoided had she not experienced this interruption in treatment. Patient 31 had experienced more than 13 emboli over a period of 50 months before starting therapy.

He was treated uneventfully for 27 months but developed a splenic infarction, as determined clinically, during the twenty-eighth month. Three weeks later he died and at autopsy splenic arterial occlusion and infarction were confirmed; however, the heart and aorta were free of mural thrombus material or any apparent endothelial roughening.

Patient 5 experienced a possible brachial embolism during her fourteenth month of treatment, and patient 25 incurred a splenic infarct during the fiftieth month of therapy.

Emboli After Cessation of Anticoagulation: The anticoagulant therapy in 23 "patient-courses" has been discontinued (table 2), 17 of the patients being available for follow-up study. In five of these individuals (patients 1 to 5) there have been no subsequent embolic episodes. Each of the other 12 persons has had at least one embolus, with a total of 14 embolic complications since therapy was stopped. Four emboli have occurred within the first two weeks after anticoagulants were discontinued, four developed during the third and fourth weeks, and six took place between the third and twenty-third months after therapy was discontinued. Patient 9 experienced

TABLE III
The Effect of Anticoagulant Therapy on the Incidence of Embolism

	Number of Emboli	Patient-months
Before Anticoagulant Therapy	103	275
During Anticoagulant Therapy	13	625
After Cessation of Anticoagulant Therapy	14	239

a fatal cerebral embolism, and patient 8 incurred a permanent hemiplegia and aphasia.

Thus, in 71 per cent of the cases in which long-term anticoagulant therapy was stopped a complicating embolism has occurred, one fatal and another seriously crippling. These 14 emboli have taken place within a follow-up period of 239 patient-months since stopping the anticoagulants.

A comparison of the incidence of embolism before, during and after anticoagulant therapy in relation to patient-months is summarized in table 3.

Currently Under Treatment: There are 12 patients currently receiving continuous anticoagulant therapy with Dicumarol. At present all such individuals have been advised that this program of treatment should be continued for at least several years, possibly indefinitely, or until such time as they become faced with a contraindication to anticoagulation.

Anticoagulation: Thus, anticoagulants have been administered for a total of 625 "patient-months" with only one instance of serious hemorrhage. Some patients (patients 14, 20, 21, 24, 27, 28 and 25) have been treated continuously for as long as 24, 30, 32, 44, 46, 55 and 56 months, respectively.

DISCUSSION

Clinical embolism occurs in between 4 and 8 per cent of patients with rheumatic mitral stenosis,^{1,2} and seems to be increased in those individuals in whom auricular fibrillation has developed.⁷ Of this selected group who experience embolism, somewhat more than half will have multiple episodes of embolism.⁸ In addition, there are the occasional patients who suffer many episodes, some seriously disabling. The central nervous system is the most frequent site in which emboli lodge, as well as the most serious both as to immediate mortality and crippling sequelae. Since no clinical test can predict reliably the future occurrence of embolism or distinguish the individual who will experience one or multiple embolic episodes, it is the patient who has already demonstrated an embolic tendency to whom long-term anticoagulant therapy may offer significant benefit. The mere presence of auricular fibrillation or mitral stenosis without embolism does not as yet justify the initiation of chronic anticoagulant treatment.

It is difficult to present a comparative study of this type which is quantitatively and statistically valid as an index of the benefits produced by anticoagulants. Although there are individuals (patient 17 in particular) in whom embolism continues to occur despite therapy, in most instances recurrent embolism seems to be reduced or prevented during the time of continuous prophylactic administration of Dicumarol. Prior to institution of anticoagulation, the patients in this study had experienced 103 definite embolic episodes over a period of 275 "patient-months." As shown in table 3, during Dicumarol therapy 13 emboli have occurred in a period of 625 "patient-months." Four of these 13 emboli occurred within the first six week period of therapy. Daley and his associates⁹ have also observed a failure early in the course of prophylactic therapy, in that one of their five patients in a similar study experienced an embolus two months after treatment began, despite presumably adequate Dicumarol therapy. It is probable that the sources of those emboli which occur within such a relatively short time of the start of anticoagulation are intracardiac thrombi which were formed prior to and were still present at the time of institution of anticoagulation.

In other patients who have incurred an embolus later in the course of presumably satisfactory anticoagulant administration, it must be presumed that the anticoagulant alteration of the clotting mechanism was not sufficient to prevent the further formation of intracardiac thrombi. Despite these failures, the use of anticoagulants appears to be a proper and rational therapeutic step in an attempt to inhibit the deposition of additional thrombi in the heart chambers, particularly the more recently formed red thrombus substance, which is more friable and easily detached.

Additional evidence that anticoagulant therapy may exert a helpful prophylactic measure is afforded by analysis of the 17 patients in whom Dicumarol treatment had been discontinued (table 2). Approximately

three fourths of this group experienced another embolus during the following weeks or months. Only 29 per cent of those in whom treatment has been stopped have had no subsequent complicating embolism.

The incidence of embolism following cessation of long-term Dicumarol raises the possibility that a state of hypercoagulability of the blood might be engendered following withdrawal of Dicumarol from individuals to whom it had been given for prolonged periods. Certain observations have been conducted along this line to evaluate the possibility of such "rebound" phenomena. The one-stage whole plasma prothrombin time test⁸ has failed to show any hyperprothrombinemic tendency in the 10 patients who have been removed from Dicumarol therapy after periods of more than six months; in another patient, two stage prothrombin assay and Factor V assay did not indicate an accelerated clotting tendency. Similarly, no hypercoagulable changes were observed in the venous clotting time test among several such patients. However, it is entirely plausible that inappreciable alterations in the coagulation mechanism are produced by long-term therapy which, upon discontinuance of Dicumarol, may result in an excessive tendency for intravascular thrombosis, particularly in patients with such circulatory abnormalities as mitral stenosis and auricular fibrillation. As more sensitive methods are devised for measuring hypercoagulable tendencies, it may well be that the recognition of such changes will be enhanced. Thus, as a matter of caution, when Dicumarol is discontinued after a treatment period of more than four months, it seems wise to decrease Dicumarol dosage gradually over a period of several weeks, rather than discontinue treatment abruptly, with the attendant possibility of rebound hypercoagulability.

At the inauguration of this study no criteria were available as to what constituted the minimal or optimal period of treatment. The experiences of the past five years have aided in the formation of certain views with regard to duration of therapy. Because a majority of those in whom therapy was stopped have subsequently had an embolism (table 2), it appears that in these individuals a program of continuous ambulatory Dicumarol for an indefinite period should be adopted, provided therapy is relatively simply accomplished and is without serious risk.

It is believed that an attempt should be made to produce reversion to regular rhythm during or prior to cessation of a protracted course of anticoagulants in patients who have already demonstrated the presence of intracardiac clot by previous embolization.

Since it has been found that thrombus material is restricted to the left auricular appendage alone in somewhat less than 50 per cent of patients with mitral stenosis and left sided intracardiac mural thrombi,^{3, 4, 9, 10} it would seem that chronic anticoagulation offers a sounder and more physiologic approach to the problem of recurrent embolism than does ligation and resection of the auricular appendage. Furthermore, Leonard and Cogan,¹⁰ reporting that three of the eight patients operated upon have experienced post-

operative embolism, conclude that medical measures seem more appropriate than surgery for this problem at the present time.

The psychologic reactions of these persons to long continued therapy have been highly gratifying. Except in rare instances coöperation has been excellent, especially with regard to their faithfulness in reporting for their prothrombin tests. In particular, those who had previously experienced repeated emboli have achieved a considerable feeling of confidence and optimism from the protection afforded by the anticoagulants, in sharp contrast to the former fatalistic outlook which several had taken toward the possibility of further potentially disabling or lethal emboli.

It should be emphasized that they have carried on their usual daily activities in the home and at business throughout the city. During the summer it has been possible for them to be away from the city without prothrombin checks for a two or three weeks' vacation without complications.

SUMMARY

In an attempt to prevent or to reduce the incidence of recurrent embolism, protracted anticoagulant therapy on an ambulatory basis has been carried out in 35 patient-courses among 28 patients who had already experienced one or more emboli of intracardiac origin.

Although there are individuals in whom embolism continues to occur despite anticoagulant treatment, comparison of the clinical courses prior to institution of therapy and during long-term anticoagulant therapy suggests a beneficial effect from the latter. One hundred three emboli had occurred during 275 patient-months prior to such treatment; 13 emboli have occurred during 625 patient-months under therapy. There are certain individuals who seem to be considerably benefited.

Furthermore, approximately three quarters of the 17 patients in whom long-term use of the anticoagulant has been discontinued have suffered another embolism after cessation of Dicumarol treatment, i.e. there were 14 embolic episodes in 239 patient-months. Thus, at the present stage of our knowledge it appears that once an individual has demonstrated a propensity to recurrent embolism for which prophylactic anticoagulant treatment has been administered, this therapy should be continued for an indefinite period.

Since it has been shown that thrombi are restricted to the left auricular appendage alone in somewhat less than 50 per cent of patients with mitral stenosis and left sided intracardiac mural thrombus, it appears that chronic anticoagulant treatment offers a sounder and more physiologic approach to the problem of recurrent embolism than do ligation and resection of the auricular appendage.

Chronic ambulatory administration of anticoagulants is practical and safe provided there are careful professional supervision and reliable laboratory control. This group of patients has received Dicumarol for a combined total of 625 patient-months, with only one instance of major hemorrhage.

BIBLIOGRAPHY

1. Kohn, C. M., and Levine, S. A.: An evaluation of the use of quinidine sulfate in persistent auricular fibrillation, *Ann. Int. Med.* **8**: 923, 1935.
2. Parkinson, J., and Campbell, M.: Quinidine treatment of auricular fibrillation, *Quart. J. Med.* **22**: 289, 1928.
3. Daley, R., Mattingly, T. W., Holt, C. L., Bland, E. F., and White, P. D.: Systemic arterial embolism in rheumatic heart disease, *Am. Heart J.* **42**: 566, 1951.
4. Graef, I., Berger, A. R., Bunin, J. J., and de la Chapelle, C. E.: Auricular thrombosis in rheumatic heart disease, *Arch. Path.* **24**: 344, 1937.
5. Harvey, E. A., and Levine, S. A.: A study of uninfected mural thrombi of the heart, *Am. J. M. Sc.* **180**: 365, 1930.
6. Garvin, C. F.: Mural thrombi in the heart, *Am. Heart J.* **21**: 713, 1941.
7. Hay, W. E., and Levine, S. A.: Age and auricular fibrillation as independent factors in auricular mural thrombi formations, *Am. Heart J.* **24**: 1, 1942.
8. Shapiro, S., Sherwin, S., Redish, M., and Campbell, H. A.: Prothrombin estimation: a procedure and clinical interpretation, *Proc. Soc. Exper. Biol. and Med.* **50**: 85, 1942.
9. Jordan, R. A., Scheifley, C. H., and Edwards, J. E.: Mural thrombosis and arterial embolism in mitral stenosis. A clinicopathologic study of fifty-one cases, *Circulation* **3**: 363, 1951.
10. Leonard, F. C., and Cogan, M. A.: Failure of ligation of the left auricular appendage in the prevention of recurrent embolism, *New England J. Med.* **246**: 733, 1952.

THE RELATIONSHIP BETWEEN PERIARTERITIS NODOSA AND SARCOIDOSIS *

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IN their recent article, Churg and Strauss¹⁴ again called attention to the fact that they have found, in additional chronic cases of periarteritis nodosa, not only the typical vascular lesions but also extravascular granulomas.

The purpose of this study is to review five autopsied cases of periarteritis nodosa and one case of sarcoidosis proved by biopsy. We would also like to consider the etiologic, clinical and histologic similarities between these two conditions, hitherto considered as distinctly separate entities.

CASE REPORTS

Case 1. This 21 year old white male was perfectly well until two days prior to admission, when he developed pain and swelling of his joints and began to vomit. He also began to complain about generalized, nonspecific abdominal pain and malaise, and became dull and apathetic. On admission to the hospital he continued to complain of pain in the abdomen, knees and small joints.

Physical examination showed an undernourished young white male with abdominal discomfort and flushed face. Positive pertinent findings were: injected throat, embedded tonsils and a soft systolic murmur over the mitral area. The abdomen was moderately tympanitic, and tender throughout to touch; the area of greatest tenderness was over the right lower quadrant. Temperature was 99.6° F. Lungs were normal. Both knees and the right wrist were tender and swollen. Red macules ranging from 2 to 5 mm. in diameter, which later became pustular, were seen on the anterior portions of both tibiae.

Laboratory: White blood cells, 26,000; neutrophils, 86; eosinophils, 1; hemoglobin, 97 per cent; non-protein nitrogen, 41; platelets, 105,000. Urine showed trace of albumin. Agglutination tests were negative. X-ray of chest and abdomen was negative. Electrocardiogram was negative.

Hospital Course: The clinical diagnosis was rheumatic fever, acute. During his hospital stay the patient received a blood transfusion, sulfonamides, penicillin, intravenous sodium salicylates and aspirin. The red blood count was between 3.5 and 4 million, the white count approximately 21,000 to 25,000, with essentially no change in the differential. Patient continued to vomit and to pass blood per rectum, and his fever remained elevated around 101° F. His condition became worse, and he went into shock and died on his twelfth hospital day.

Postmortem Examination: Positive gross findings were: gastric ulcer, gastrointestinal hemorrhage, bilateral pulmonary edema, mild cerebral edema.

Microscopic Examination: There was a leukocytic infiltration of the epicardium with lymphocytes and plasma cells. There was an extravascular granuloma consisting of epithelioid cells but without giant cells (figure 1A). The bowels showed marked perivascular and vascular inflammatory changes with hyalin in the lumen. There was

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also an extravascular granuloma present, consisting of lymphocytes and epithelioid cells (figure 1B). Some sections of the small arterioles of the bowel showed thickening, edema and infiltration with inflammatory cells through the submucosa. There was perivascular leukocytic reaction.

Final Diagnosis: Acute arteritis and periarteritis involving the small bowel, with ulceration and secondary hemorrhage; periarteritis involving the epicardium and extravascular granuloma in the epicardium; periarthritis of the skin of the extremities; petechial hemorrhage of the skin of the lower legs and feet, shoulders and arms.

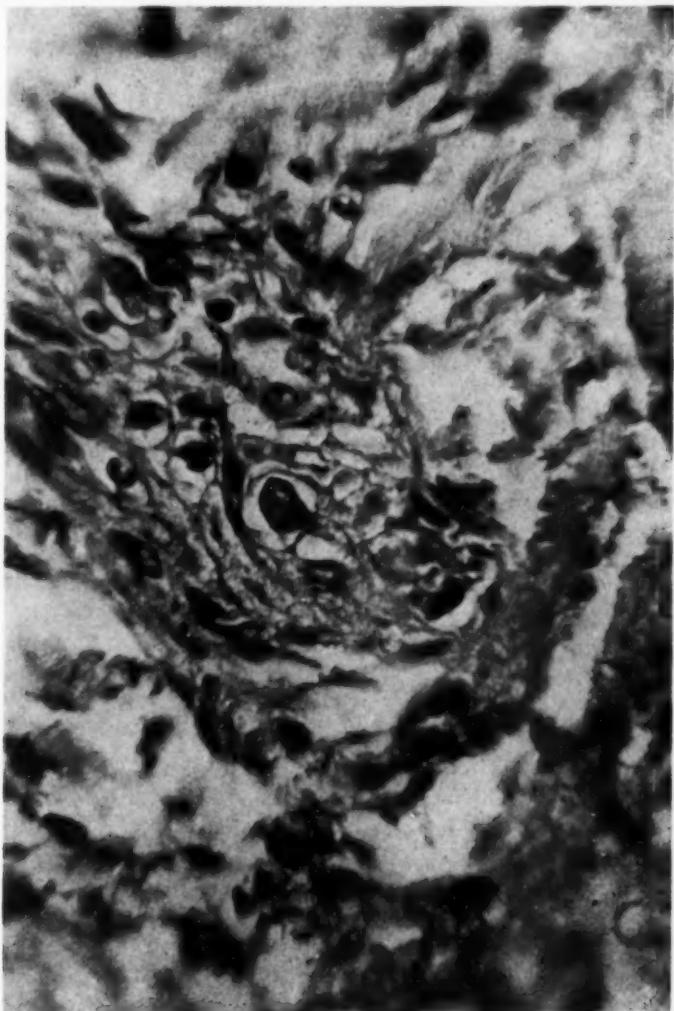


FIG. 1A. Subepicardial granuloma. (Magnification 225 \times)

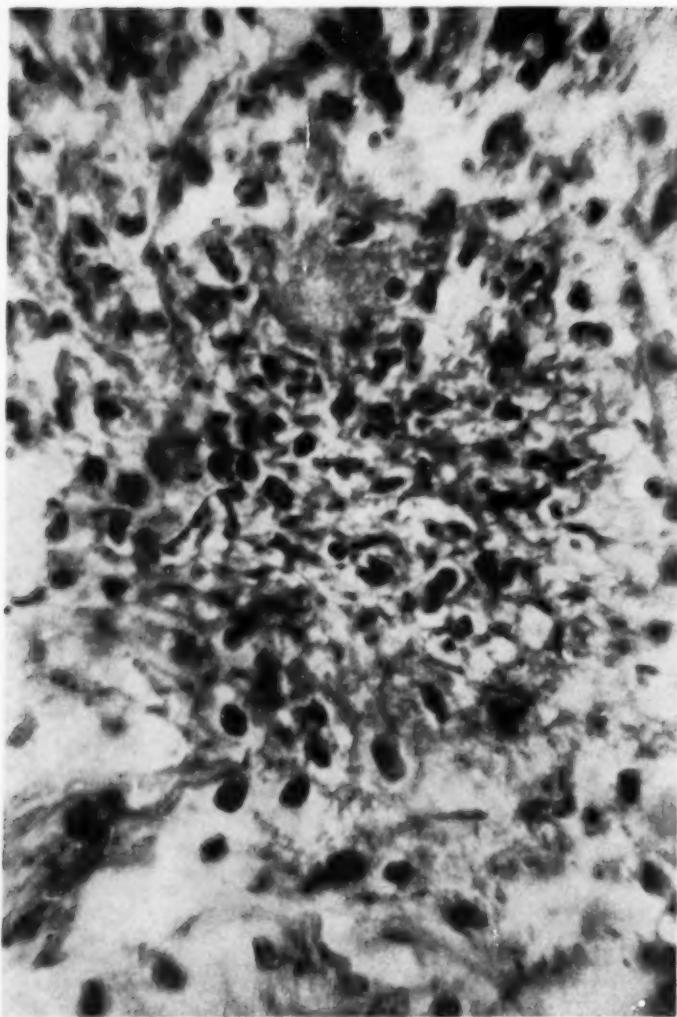


FIG. 1B. Bowel. Granuloma in the submucosa.

Comment: This was a case of periarteritis nodosa with gastrointestinal, joint and skin involvement in a person treated with sulfonamides, penicillin and salicylates. There were widespread vascular and extravascular granulomas, although the latter had no giant cells.

Case 2. This 54 year old white male was admitted to the hospital with the chief complaint of precordial pain and shortness of breath on exertion which had started

approximately one month prior to admission. He had also noticed an occasional swelling of his ankles. He gave a history of chronic alcoholism and a recent episode of cardiac decompensation. There was no history of rheumatic fever, joint pain or hypertension.

Physical Examination: Undernourished white male, slightly dyspneic. The heart was markedly enlarged to the left. The apex was in the sixth intercostal space 1 inch outside the midclavicular line. There was a loud, blowing systolic apical murmur. Auricular fibrillation with a pulse deficit, and venous engorgement of neck veins were present. The liver was enlarged two fingerbreadths beneath the costal margin. There was 2 plus pitting edema of the ankles. Clubbing of the fingers and great toes of both feet was noted.

Laboratory: Electrocardiogram showed auricular fibrillation. On one occasion the patient had a bigeminal rhythm. X-ray of the chest showed cardiac enlargement. Gastrointestinal series and barium enema were normal. Urinalysis was normal. Blood count was normal. Platelets were normal. Hematocrit was normal. Non-protein nitrogen on admission was 44. Venous pressure was 50 mm. of H₂O. Circulation time was: saccharine, 40 seconds; ether, 15 seconds.

Hospital Course: During his hospital stay the patient responded at first to routine cardiac management but later on became decompensated. He was treated with Crystodigin, aminophylline and Mercuhydrin. He developed large ecchymotic spots on both arms and the abdominal region which lasted for a few weeks and then disappeared. Patient had a sudden onset of dyspnea and died within a few minutes.

Postmortem Examination: Pertinent findings were: generalized periarteritis nodosa; infarction of kidney; myocardial fibrosis; emphysema; chronic passive congestion of liver and spleen.

Microscopic Examination: Many arteries (adrenals, lungs, kidneys, testes) showed infiltration of the media with lymphocytes and plasma cells. The adventitia was infiltrated with lymphocytes. Some of the arteries showed complete occlusion. Dissection through all organs showed many arteries with typical lesions of periarteritis nodosa. Extravascular granulomas consisting of epithelioid cells and lymphocytic infiltration with giant cells were present in the liver and bowels (figures 2A and 2B). Areas of proliferation and thickening and round cell infiltration were noticed around the veins.

Final Diagnosis: Generalized periarteritis nodosa; infarction of kidney; myocardial fibrosis.

Comment: This case showed the typical lesions of periarteritis nodosa, with purpura hemorrhagica; vascular and extravascular granulomas with giant cell formation. Whether the periarteritis nodosa was due to sensitivity to Mercuhydrin it is impossible to tell.

Case 3. This 52 year old colored male was perfectly well until about six weeks prior to admission, at which time, upon awakening, he noticed some weakness of his left knee and leg and swelling of his ankles. The swelling progressed until he developed a generalized anasarca. He had severe headaches. He was treated with both penicillin and sulfonamides. There was no dyspnea or orthopnea. No limitation of motion of his joints was noted. His symptoms disappeared after two or three days. About three weeks prior to admission he began to develop a fever almost daily.

Physical Examination: Chronically ill, cachectic appearing colored male who showed evidence of recent weight loss. Blood pressure, 130/82 mm. of Hg. The heart was not remarkable; there were no murmurs or arrhythmias. The liver, spleen and kidneys could not be palpated. There were no areas of muscle guarding or

tenderness. The testicles were atrophic. The epididymides were tender, enlarged and firm but not definitely nodular. There was pitting edema of both ankles.

Laboratory: X-ray of chest was negative. Gastrointestinal series was normal. X-rays of the pelvis and lumbar vertebrae were normal. Routine examinations for typhoid and paratyphoid were negative. Non-protein nitrogen was 31.6. Sedimentation rate was 102. Specific gravity of the urine was 1.010. The red blood cell count was 3,130,000; white blood cells, 19,000, with 88 per cent neutrophils, 13 per cent lymphocytes, 1 per cent eosinophils. Wassermann test, 3 plus; Kahn test, 4 plus.

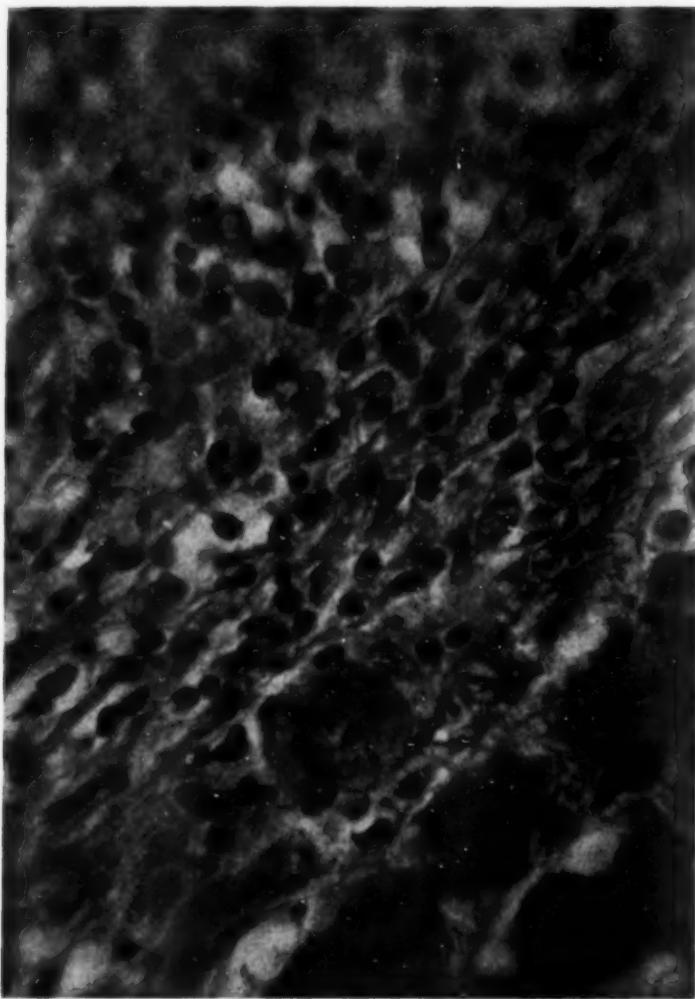


FIG. 24. Liver. Subcapsular granuloma with giant cell.

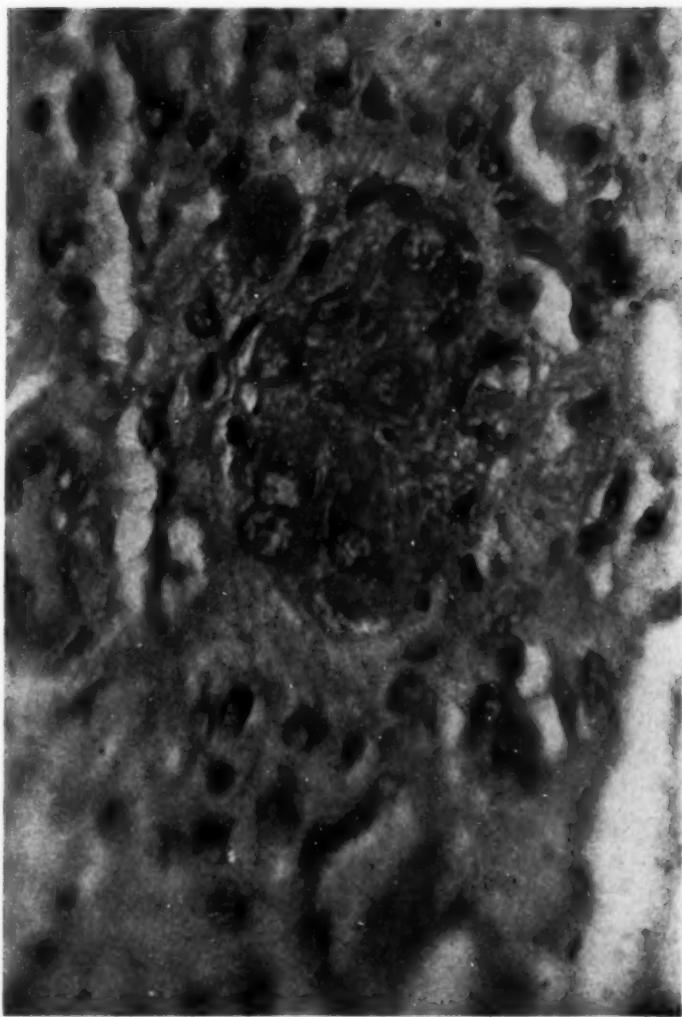


FIG. 2B. Bowel. Granuloma in the submucosa with giant cell.

Hospital Course: The albuminuria continued and the red blood count became depressed. The white blood count and non-protein nitrogen became elevated. Terminally the non-protein nitrogen was 182.9 mg. per cent; creatinine, 10.4 mg. per cent; uric acid, 12.4 mg. per cent; chlorides, 420 mg. per cent; calcium, 10 mg. per cent; cholesterol, 150 mg. per cent; phosphorus, 3.6 mg. per cent; total protein, 7.3 gm. per cent; albumin, 4.9 gm. per cent; globulin, 2.4 gm. per cent. Electrocardiogram showed myocardial damage. Blood was negative for sickling. Chief complaint was

generalized pain. He was febrile. It was felt that patient had a nephritis following a systemic infection. He became comatose and died with the picture of terminal uremia.

Postmortem Examination: The heart was covered with fibrinous exudate; it weighed 410 gm. The coronary arteries were patent. The parenchyma of the right kidney was compressed by one large cyst connected to the pelvis. The cortex of the left kidney was thin.

Microscopic Examination: In the prostate the arteries showed a marked thickening of their walls, with almost total obliteration of the lumen and fibrous tissue replacement in the vessel walls. Varying stages of periarteritic involvement were noted, the most frequent being the fibrotic one. The testicles showed widespread infarction, with numerous periarteritic lesions and extensive fibrous tissue replacement. Again varying stages of periarteritis nodosa were encountered. The pancreas showed diffuse periarteritis, with inflammatory cells scattered throughout the parenchyma. There was marked thickening of the walls of the vessel, with replacement by fibrous tissue and infiltration of the vessel walls by inflammatory cells, mainly lymphocytes. There were also extravascular granulomas present, consisting mainly of epithelioid cells (figure 3A). The liver showed extensive areas of necrosis and degeneration. A large vessel was completely occluded by an organized thrombus. The kidneys showed periarteritic changes of the vessels. There were also extravascular granulomas present in the collagenous tissue consisting of epithelioid and giant cells (figure 3B). The adrenals and spleen showed periarteritic changes of the smaller arteries.

Final Diagnosis: Widespread and generalized periarteritis nodosa involving the prostate, testicles, pancreas, liver, spleen and kidney and, to a much lesser degree, the lungs, heart and adrenal gland; infarction of the testicles and kidneys due to arterial occlusion from periarteritic lesions.

Comment: This was a case of periarteritis nodosa in a patient treated with sulfonamides and penicillin. There was an infarction of the testicles and kidneys, as well as widespread typical vascular lesions. Extravascular granulomas consisting of epithelioid and giant cells were observed.

Case 4. This 61 year old colored male was admitted to the hospital complaining of headaches and sore nose of two years' duration. Ten years before he had sustained a head injury and had been unconscious for several hours, and since then he had had frontal headaches, aggravated by coughing and sneezing and relieved by aspirin. There was no history of nausea, vomiting or visual disturbances. Systemic review revealed a moderate cough of several years' duration, moderate constipation, and occasional precordial pain on exertion. Patient stated that during the past two years he had had several episodes of chilly sensation followed by fever, lasting eight to 10 days.

Physical Examination: A well developed, well nourished colored male in no acute distress. He had a well healed, nontender scar in the right occipital region. Blood pressure, 140/100 mm. of Hg. There was atrophy of the left testicle. Left abdominal reflexes were absent. The right patellar reflex was less active than the left.

Laboratory: Urinalysis revealed several white blood cells per high power field. Serologic tests for syphilis were negative; serum amylase was normal. All agglutination tests were normal. Spinal fluid examination was normal. Serum bilirubin was 0.6; non-protein nitrogen, 29 mg. per cent; total protein, 5.5 gm. per cent; red blood cells, 4,200,000; white blood cells, 5,000 on admission, and later 29,000. Hemoglobin, 74 per cent on admission, dropping later to 58; eosinophils varying from 2 to 5 per cent. Sedimentation rate was 104. X-ray of the chest was normal. X-ray of paranasal sinuses showed slight haziness of the maxillary antrum. X-ray of skull

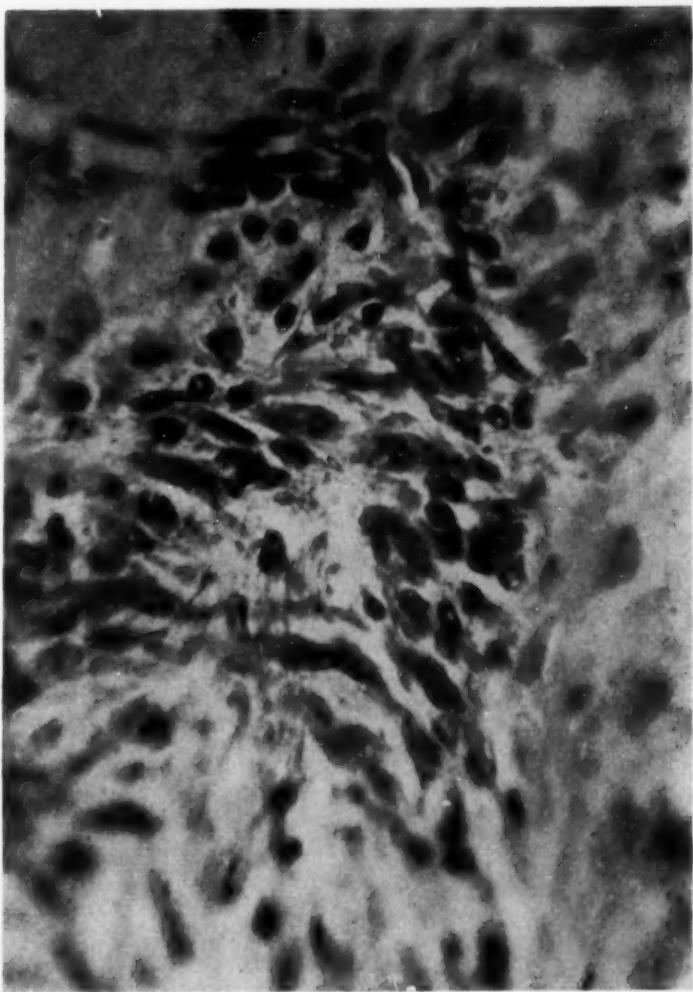


FIG. 3A. Pancreas. Interlobular granuloma.

showed a small plaque of calcium in the wall of the falx cerebri. A scout film of the abdomen showed no obstruction. Barium enema was normal. Electrocardiogram was normal except for ventricular premature contractions.

Hospital Course: On admission the temperature was normal, but later the patient began to develop fever despite penicillin therapy. On the seventh hospital day he developed a transient abdominal pain which was followed by nausea and vomiting. He experienced a similar episode the following morning. The abdomen was dull and rigid in the left lower flank. The patient was given streptomycin and blood trans-

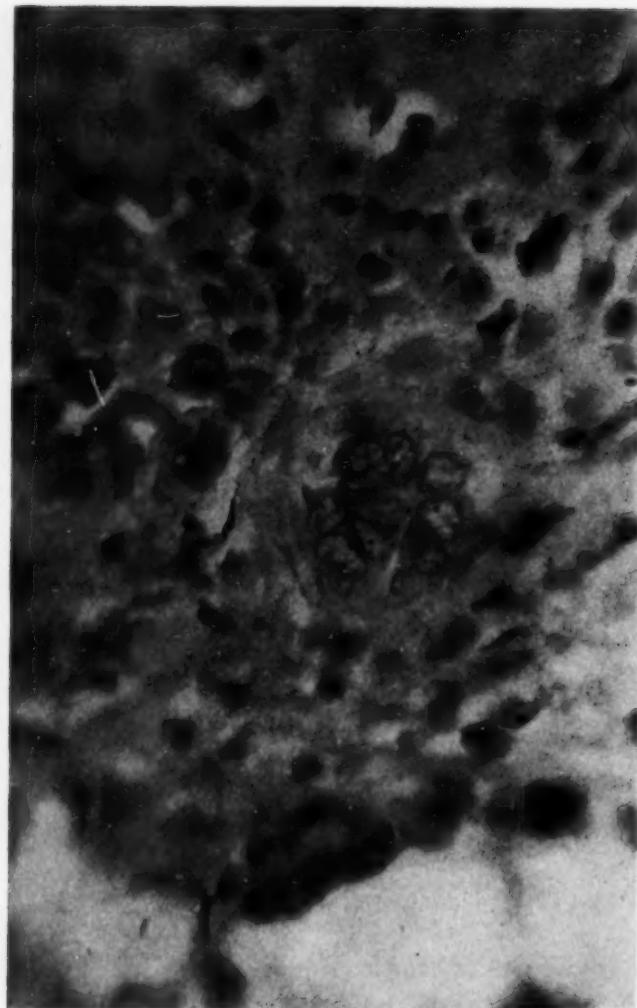


FIG. 3B. Kidney. Interstitial granuloma with giant cell.

fusions. An exploratory laparotomy was performed. The abdomen was negative except for a slight enlargement of the left kidney. Patient suddenly died.

Postmortem Examination: The pericardial sac contained about 100 c.c. of clear yellowish fluid. The heart weighed 380 gm. and was normal. The aorta showed a moderate amount of arteriosclerosis. The adrenals appeared small and their cortex thin. The right kidney weighed 240 gm.; left, 310 gm. The glomeruli were distinct. The cortex measured 4 mm., the medulla 15 mm. in thickness. The testicles were

atrophic and small. The gastrointestinal tract was normal, except that the mesentery contained minute nodular growths which could be felt between the fingers.

Microscopic Examination: The coronary arteries showed an advanced degree of obliterative change as well as extensive fibrous tissue replacement of their walls. The lumen of some vessels was almost obliterated by this change. The entire wall showed an infiltration with lymphocytic and plasma cells. The pancreas showed fibrotic areas in which the vascular channels showed varying degrees of obliterating changes associated with extensive inflammatory reaction involving all layers of the vessel wall. There was a marked lymphocytic and plasma cell infiltration. The spleen showed the same generalized periarteritic involvement. The glomeruli were small, an occasional one hyalinized. The renal vessels all showed advanced inflammatory changes. There was an extreme atrophy of the testicular parenchyma. The adrenals showed considerable parenchymatous degeneration, and there were both inflammatory and fibrotic vascular changes. The aorta showed a moderate degree of hyalinized intimal thickening. In the fat tissues, beginning extravascular granulomas were observed (figure 4).

Final Diagnosis: Generalized periarteritis nodosa; atrophy of the testicles; chronic nephritis.

Comment: This was a case of periarteritis nodosa treated with penicillin and streptomycin in which a fever of undetermined origin was the first clinical manifestation.

Case 5. Patient's first admission to the hospital was on January 25, 1946. He was complaining of anginal pain. Electrocardiogram revealed evidence of posterior infarction. The patient improved and was discharged. He was readmitted to the hospital in 1947 complaining of chest pain which radiated down his arms. At that time physical examination showed an obese male, not acutely ill. Blood pressure, 118/76 mm. of Hg. Cardiac examination was essentially negative. Peripheral vessels were slightly thickened but not tortuous. Electrocardiogram showed evidence of an old posterior infarction. He was placed on a reducing diet and discharged. The patient's next admission was in September, 1949, at which time he complained of pain in his chest and fever.

Physical Examination: A 54 year old white male in no acute distress, weighing 200 pounds. Eye grounds showed minimal degree of retinal arteriosclerosis. Blood pressure, 114/76 mm. of Hg. Electrocardiogram showed an old posterior wall infarct. Routine urinalysis was negative. Hemoglobin was about 85 per cent. White count and differential were within normal limits. Serologic tests for syphilis and agglutination tests were negative. Non-protein nitrogen was 49 mg. per cent. Sedimentation rate was 110. Urine cultures separately from each kidney were negative. Blood cultures were negative. Feces were negative. Spinal fluid examination was negative. X-ray films of skull were negative. X-ray of chest was negative. Gastrointestinal series and barium enema were negative with the exception of the prolapse of the gastric mucosa into the duodenal bulb. Retrograde pyelograms showed a dilatation of the right renal pelvis and upper two thirds of the right ureter.

Hospital Course: Patient continued to have fever. The diagnosis was obstruction of the right ureter. He was operated upon and scar tissue approximately 5 cm. in diameter was dissected off the ureter. Biopsy of the tissue showed dense old hyaloid connective tissue with lymphocytic infiltration and a blood vessel the center of which had undergone complete occlusion from an old thrombosis. Patient continued to run a fever. In April, 1950, he developed a swelling of the left testicle which was diagnosed as a hydrocele. Patient continued to have anginal pain. He

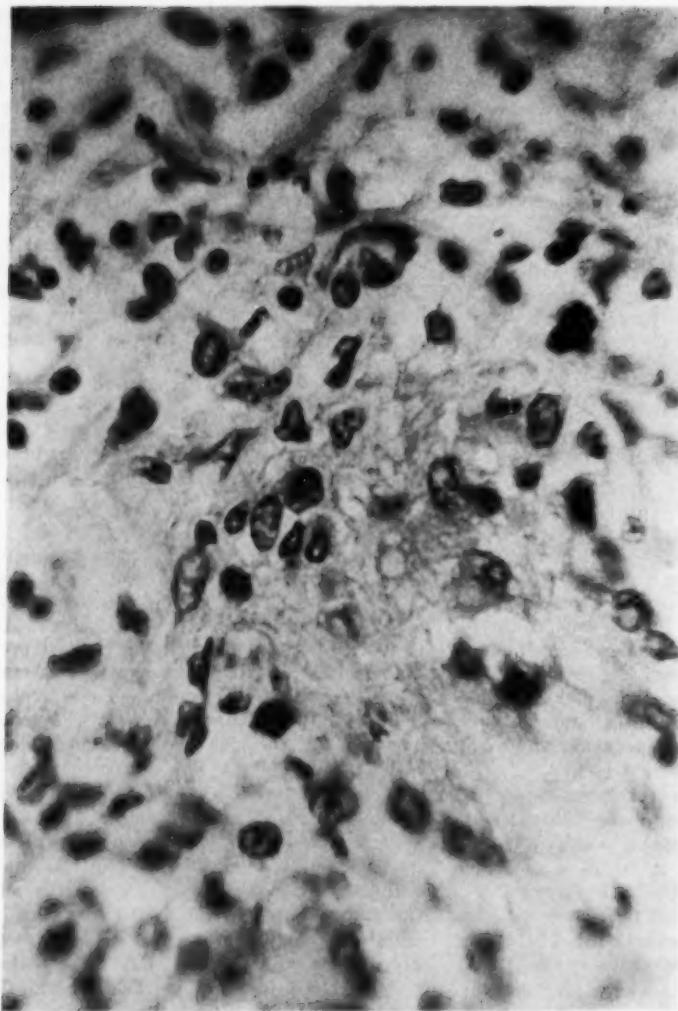


FIG. 4. Granuloma in the perilymphnodal fat tissue.

died on November 10, 1950, complaining of pain in the chest. A bottle of nitroglycerin was found near his bed.

Postmortem Examination: Heart: The coronary arteries were surrounded by thick, hyaline gray tissue. The anterior descending artery and the right circumflex artery were occluded. The myocardium showed a purplish discolored area in the anterior portion of the left ventricular wall and patchy areas in the posterior aspect of the left ventricular wall. The aorta showed a moderately severe arteriosclerosis

with calcific plaques in its abdominal portion. There was a thick cuff around the aorta measuring 8 cm. in thickness, extending from 5 cm. above the bifurcation down into the iliac vessels, fusing with the fibrous hyaline masses surrounding the common iliac vessels, hypogastric vessels and ureters. There was obstruction of the left ureter near the pelvis, where the inflammatory mass surrounding the aorta and common iliac vessels also incorporated the ureters. The renal arteries showed the same nodular, hyaline gray thickening seen in the other arteries. There was a hydrocele of the left testicle.

Microscopic Examination: A section of the right circumflex coronary and anterior descending artery showed a large cuff of thick bands of hyaline fibrous tissue coursing in various directions. Between these bands were multiple collections of plasma cells and lymphocytes and an occasional large clump of lymphocytes. The intimal thickening was sufficient to obliterate the lumen and create an organized thrombus. Near a great vessel there was granulomatous tissue consisting of epithelioid cells and lymphocytes but without giant cells (figure 5). Multiple sections of many of the other larger arteries throughout the body showed the same thickening. This was particularly marked in the lower portion of the abdominal aorta and bifurcation of the first part of the common iliac arteries. Cross section of the splenic artery showed a very large cuff almost entirely surrounding it.

Final Diagnosis: Periarteritis nodosa; coronary occlusion with acute and chronic myocardial infarction; hydronephrosis and hydro-ureter, left; hydrocele of the left testicle.

Comment: This was a case of periarteritis nodosa involving only the aorta and its major branches. Extravascular granulomas were present. There was no detectable extrinsic or intrinsic hypersensitivity agent.

Case 6. This 22 year old Negro male was discharged from the Army in 1947 in good health. In 1948 he had a short episode of dyspnea and productive cough. He was first admitted here on September 29, 1948, and a diagnosis of bronchial asthma was made. Chest x-ray taken at that time was negative. Following discharge he continued to have slight dyspnea on exertion and an occasional cough but was able to work regularly. About three months before his last admission patient developed an evening fever (up to 103° F.) which continued for several weeks. There was no asthma and no increase in severity of the cough at that time. Fever subsided spontaneously. At the time of admission (February 7, 1950) the patient complained of slight dyspnea on exertion, productive cough containing a small amount of clear sputum, substernal discomfort following exertion and a constant bad taste in his mouth. There was no weight loss, general malaise or anorexia.

Physical examination revealed a well developed, slightly undernourished Negro male who was comfortable at rest. There was decreased resonance in the right axillary region, and fine râles were heard in the same area. Distant wheezing was heard throughout the chest. The heart and abdomen were normal. There was no clubbing of the fingers or lymphadenopathy.

Laboratory: Routine serology, urinalysis and hematology were normal (4 eosinophils). Sedimentation rate was 110. Total protein was 7.7; albumin, 4.3; globulin, 3.4; A/G ratio, 1.3; calcium, 11.6; inorganic phosphorus, 5.2. Cold agglutinins were normal. Sputum culture grew *Streptococcus viridans* and beta hemolytic streptococcus. Sputum cultures for fungi and tubercle were negative. Tuberculin, histoplasmin and coccidioidin skin tests were negative. X-ray studies of the chest showed extensive irregular, somewhat nodular densities throughout each lung field. There was also evidence of hilar adenopathy. X-rays of both hands and feet, intravenous pyelograms and gastrointestinal series were negative.

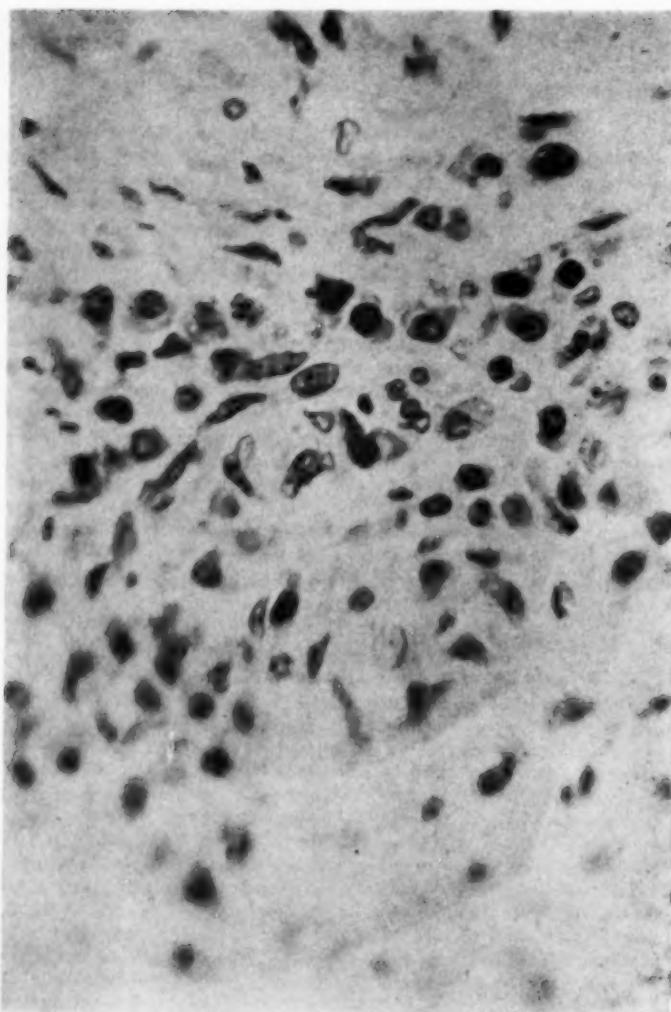


FIG. 5. Granuloma in the perivascular fat tissue.

Hospital Course: During the second hospital admission the patient ran an occasional slight fever. A diagnosis of pulmonary sarcoidosis was entertained; however, since there were no palpable glands, it was impossible to make a histologic diagnosis.

In July, 1950, several subcutaneous nodules appeared. The patient at the time was in another city. A biopsy of a node was done and the histologic diagnosis of Boeck's sarcoid was made. A copy of the biopsy report was forwarded to our hospital.

Comment: This patient had a fever of undetermined origin, a high sedimentation rate and bronchial asthma. No nodes appeared for two years. This case might easily have been diagnosed as periarteritis nodosa.

DISCUSSION

Periarteritis nodosa is still a rare disease. Approximately 350 cases were reported through 1942.⁷⁶ The total number of cases in spite of numerous publications is still probably not over 1,000. At one time periarteritis nodosa was thought to be rare in infancy and childhood; however, about 100 cases of periarteritis in childhood have been reported. There is no etiologic or morphologic difference between periarteritis nodosa in childhood and in adults.¹ Whether this disease is on the increase or whether physicians are now more aware of this condition and diagnose it more frequently than before is difficult to tell; the latter is probably more nearly correct.

Meier's original article⁵³ enumerated symptoms such as chlorotic marasmus, polyneuritis, polymyositis and abdominal symptoms as characteristic of periarteritis nodosa. Later on Brinkman added nephritis. Subsequently Solomon, Kasich and Kiven⁹¹ divided the manifestations of periarteritis nodosa into four groups: (1) findings related to the inflammatory process, such as fever, leukocytosis, malaise, anemia, increase in sedimentation rate corresponding to a picture of fever of unknown origin; (2) symptoms arising from involvement of the arteritis of each organ in question, such as heart, nervous system, kidney, etc.; (3) findings of allergic manifestations such as eosinophilia; (4) positive skin biopsy.

Hypertension⁴⁷ had been thought to be an etiologic factor in periarteritis nodosa. It had been advocated that hypertension with accompanying high blood cholesterol and anoxia may favor the disruption of the vascular wall. However, Wilens et al.,¹⁰⁷ in the study of 100 cases of periarteritis nodosa, found that in 50 per cent of the cases hypertension was not present. Many patients with periarteritis nodosa developed hypertension at the later stages of the disease, and others had renal lesions of periarteritis nodosa which might well have been responsible for the hypertension. Wilens concluded that hypertension was not a factor in periarteritis nodosa. Ehrlich,²³ in his very comprehensive article on the collagen diseases, stated that hypertension in human periarteritis nodosa was secondary to renal involvement. Rose⁷⁸ stated that hypertension may occur as a late complication in periarteritis nodosa.

It is difficult to explain how hypertension can be a factor in pulmonary periarteritis nodosa, since the blood pressure in the pulmonary system is low.^{62, 66} Hypertension, if present, is an accessory factor in periarteritis nodosa but not an etiologic one. Equally, renal disease⁴⁸ is not a cause but a rather frequent site of involvement.

In the period when sulfonamides were so widely used, many cases of

periarteritis nodosa attributed to them were reported.^{30, 32, 55} Dilantin,¹⁰¹ thiouracil,^{6, 57} iodides,⁷³ heavy metals,⁸² bacterial toxins,³⁹ penicillin⁸ and ratbite fever⁶⁸ have been suggested as etiologic agents in proved cases of periarteritis nodosa. Trichinosis or positive trichinosis skin test has also been reported.⁶⁹ It might be noted that drugs like Mercuhydrin, Dilantin, thiouracil and sulfonamides also cause aplastic anemia, and it is possible, as suggested by Silverman and Worthen,⁶⁹ that the bone marrow becomes sensitized to these drugs and acts as a shock organ.

Gruber^{33, 34} first suggested an allergic etiology, a hypersensitivity reaction due to infection. This is now the generally accepted opinion, especially since Rich, Rich and Gregory, Selye, Matsugi and others^{22, 37, 41, 58, 70, 71, 72, 74} succeeded in experimentally producing periarteritis nodosa by injecting foreign protein in animals.

Klemperer⁵¹ states that bacteria are not the immediate cause in collagen disease, but the hypersensitivity due to bacteria or to bacterial toxins is the cause.

The combination of periarteritis nodosa with bronchial asthma and eosinophilia has been observed.^{55, 108} Wilson and Alexander¹⁰⁸ reported that bronchial asthma occurred in 18 per cent of 300 cases. Periarteritis nodosa in association with tuberculosis has been reported.¹⁵ Periarteritis nodosa also occurs concomitantly with rheumatic fever and rheumatoid arthritis.^{7, 28, 59, 74} Selye^{84, 86} produced in rats, by injecting somatotropic hormone, rheumatoid arthritis-like lesions associated with periarteritis nodosa.

Periarteritis had been considered a fatal disease of short duration. Now many cases of recovery have been reported.^{32, 50, 60, 76, 102} (Klein has reported a case with a second relapse after a 12-year interval with positive biopsy obtained the first and second time.) Since ACTH and cortisone are available, more cases of long duration and recovery will probably be reported in the future.

The reason that periarteritis nodosa has been considered as only a vascular disease is because the changes occur probably first in the blood vessel. The earliest sign of periarteritis nodosa is a subendothelial swelling.^{65, 94} Later on there are a fibrinoid exudation and necrosis of the vascular wall. If there is a breach in the vessel wall, fibrin deposition and necrosis might also be found outside the vessel and may involve the connective tissue. In addition to the perivascular foci pseudotuberculous necrotic lesions may occur in periarteritis nodosa, and granulomas resembling Aschoff bodies may develop. Pagel⁶⁵ states that polyarteritis nodosa differs from rheumatic and what he calls pararheumatic lesions (lupus, dermatomyositis, etc.) in its clinical course and in the distribution of the lesions, but the basic histologic changes appear to be identical in all. Similar observations were made by Ehrlich.²³

Most descriptions of periarteritis nodosa pertain to the arteries; however, extravascular granuloma formation is occasionally observed^{7, 35} with

infiltration of eosinophils and fibrinoid degeneration and necrosis. Also, formation of epithelioid and giant cells around the necrotic collagen has been noted.^{64, 71, 101}

Recently the subject of extravascular lesions in periarteritis nodosa has been brought again to attention by an article by Churg and Strauss.¹⁴ These authors found that in 13 cases of periarteritis nodosa with bronchial asthma (and eosinophilia) there were granulomatous lesions present in the connective tissue consisting of epithelioid cells, and giant cell reaction in addition to the typical periarteritis nodosa lesions, and, on the other hand, in 15 cases of periarteritis nodosa without bronchial asthma none had extravascular lesions and none showed epithelioid and giant cells. The authors consider the first type to be a separate entity and named it allergic granulomatosis and hypersensitivity angiitis. They state that periarteritis nodosa is a heterogeneous group and distinguish three separate entities: (1) hypersensitivity angiitis as reported by Zeek et al.¹¹⁰ (in the acute stages); (2) "true" periarteritis nodosa; (3) allergic granulomatosis in more chronic cases, seen in approximately one third of all cases of periarteritis nodosa. This division into three separate entities is not generally accepted. Ehrlich²³ thinks that it is better to consider allergic granulomatosis as a phase of periarteritis nodosa. All of our five cases of periarteritis nodosa showed extravascular granulomas in addition to the typical vascular lesions, and none of them had bronchial asthma.

Let us consider another condition—beryllium granulomas. Curtis¹⁸ states that beryllium dermatitis is a hypersensitization phenomenon rather than a reaction to the metal irritant. Susceptible patients react to a high dilution of soluble beryllium salts with a positive skin patch test. It is probable that the lesions caused by beryllium (mostly in the lungs) are like those caused by Dilantin, iodide, thiouracil, Mercuhydrin, etc., due not to the foreign body itself but to an allergic reaction in which a beryllium hapten is formed. Beryllium granulomas histologically¹⁰⁰ resemble sarcoidosis, and it is at times impossible to distinguish between these two granulomas without special stains. Beryllium granuloma has been called "pulmonary sarcoidosis." The biochemical findings in beryllium granulomas are similar to those found in periarteritis and in sarcoidosis: high globulin, also disturbance of the blood calcium and blood phosphorus and inhibition of the alkaline phosphatase.

At first glance, periarteritis nodosa and sarcoidosis appear to be two totally different entities. In the textbooks of medicine and pathology periarteritis nodosa, as the name implies, appears under the caption of diseases of the arteries—necrotizing arteritis (even if there is involvement of the vein), whereas sarcoidosis appears under the heading of the diseases of the lymphatic system because most or all granulomas of sarcoidosis involve the lymph nodes.

ETIOLOGY OF SARCOIDOSIS

Whether tuberculosis plays an etiologic rôle in sarcoidosis is questionable. But even if it does, it is not the tubercle bacillus in itself which causes sarcoidosis: the sarcoid granuloma is a hypersensitivity reaction to tuberculous toxin, the so-called positive anergy of Jadassohn. Hypersensitivity is now generally accepted to be the pathogenetic mechanism in sarcoidosis.^{17, 26, 67} Leishmaniasis,²¹ syphilis,²⁶ leprosy,²⁸ silica,²¹ trauma⁴⁶ and beryllium¹⁶ have been reported as etiologic agents in sarcoidosis. According to Teilum⁹⁵ and Rosenberg⁷⁷ sarcoidosis is due to a blockage of the reticuloendothelial system. It is assumed to be reaction of the reticuloendothelial system to the antigen with production of gamma globulin antibodies, with increase of the plasma cells, lymphocytes, leading to an increase of the serum gamma globulin and later a granulomatous reaction with epithelioid cells, plasma cells and giant cells.

According to Kissmeyer,⁴⁹ the initial process in sarcoidosis is a perivascular inflammatory reaction, consisting at first of lymphocytes; later on there are a few epithelioid cells and fibroblasts, and finally the typical epithelial cell granuloma is formed.

Curtis¹⁷ states that in sarcoidosis collections of epithelioid cells are often found in the vicinity of blood vessels. Sarcoidosis granulomas are spread by the blood stream. Riley⁷⁸ states that the extrapulmonary distribution of lesions in sarcoidosis is highly suggestive of hematogenous dissemination. Likewise, periarteritis nodosa has been considered a vascular disease in which the bloodborne antibody damages the vessel wall first and—if the patient lives long enough—extravascular granulomas, due to hematogenous spread, are formed.

Epithelioid cells are the chief component of the sarcoid granuloma. There is never caseation, as in tuberculosis. With increased age there is more fibrin deposition or, rather, hyalinosis, also called para-amyloidosis. This microscopic picture has similarities to that of periarteritis nodosa, described above. Sarcoidosis is a chronic disease and, on the whole, only late stages of the granulomas have been studied microscopically. Periarteritis nodosa, on the other hand, has hitherto been a rapid, fulminating disease and therefore only early stages have been studied. Obviously only similar stages should be compared for purposes of establishing a histologic similarity or dissimilarity. Now with ACTH and cortisone available, periarteritis nodosa will probably become a more chronic disease, and late granuloma stages of periarteritis nodosa will probably become more and more prominent.

There are many reports of rheumatic fever and periarteritis nodosa occurring concomitantly in the same person. Also, reports of rheumatic fever and sarcoidosis occurring simultaneously in the same person have been published. Thorn et al.⁸⁷ reported a case of concomitant occurrence of rheumatic fever and sarcoidosis in the same patient treated with cortisone. In

Riley's⁷⁵ 52 cases of Boeck's sarcoid, five had rheumatic fever with and without cardiac involvement.

Association of periarteritis nodosa and sarcoidosis in the same patient has been reported by Staehelin,⁹² Weinberg,¹⁰⁶ Rosenthal,⁷⁸ Gartside,²⁹ Teilum⁹⁶ and Symmers.⁹⁴ Symmers reported recently a case of periarteritis nodosa and sarcoidosis in the same person, and he states that "polyarteritis and sarcoid-like lesions are considered as morphologic manifestations of opposite and non-contemporaneous phases of allergic reactivity to the same infection."

There is also the so-called Wegener's granulomatosis,¹⁰⁴ a disease associated with hypersensitivity reported by Mallory¹² and Castleman¹³ in the Clinical Pathological Conferences of the *New England Journal of Medicine*. This disease consists of sarcoid-like lesions complicated by a disseminated necrotizing angiitis of the Zeek type.

There is, finally, another disease, or rather manifestation of disease, now universally recognized, as due to hypersensitivity, namely, erythema nodosum. Erythema nodosum has been associated with tuberculosis, coccidioidomycosis, sarcoidosis, leprosy, measles, scarlet fever, diphtheria, bromides, iodides, sulfonamide and rheumatic fever.⁴² Microscopically, erythema nodosum consists of granulomas of the connective tissue similar to those reported in sarcoidosis and to the extravascular granulomas of periarteritis nodosa. Erythema nodosum responds to ACTH and cortisone treatment.⁹⁸

The clinical picture in periarteritis nodosa and in sarcoidosis presents certain similarities, common to all systemic diseases difficult to diagnose, like weakness, malaise, loss of weight, fever, dyspnea, cough, hematuria and albuminuria.^{2, 17, 27, 36, 45, 56, 75, 76} Other similarities found in periarteritis nodosa and Boeck's sarcoid are the organs involved. In Boeck's sarcoid the lymph nodes are always involved. Next in order of frequency come the lungs and spleen.^{27, 75} In Riley's cases there was lymphadenopathy in 100 per cent. The lungs were involved in 87 per cent, the spleen in 40 per cent, the liver in 37 per cent. There were skin manifestations in 25 per cent and the fundus was involved in 2 per cent of the cases. The sedimentation rate was elevated in 78 per cent and there was eosinophilia in 24 per cent.

In periarteritis nodosa there is also frequent lymphadenopathy. Churg and Strauss¹⁴ state that there is frequent generalized lymphadenopathy in periarteritis nodosa. In one of their cases of periarteritis nodosa a lymph node removed for biopsy showed a picture suggestive of Hodgkin's disease. At autopsy numerous lymph nodes were present. In Rose's cases of periarteritis nodosa lymphadenopathy was present in 33 per cent, hepatomegaly in 50 per cent, splenomegaly in 17 per cent, and pericardial involvement in 17 per cent. Pulmonary involvement occurs in approximately 40 per cent of the cases of periarteritis nodosa.^{10, 40, 62, 66} Parenchymal lung involvement in periarteritis nodosa was observed a long time ago by Ophuls.⁶³ Even cavitation of the lungs in periarteritis nodosa has been reported by Sandler

et al.⁸² Gastrointestinal bleeding occurs in periarteritis nodosa^{9, 76, 109} and in sarcoidosis as well.⁸⁰ Nervous manifestations like foot drop have been reported in both conditions.^{75, 76, 103} The heart and pericardium^{27, 99} and the kidneys^{4, 48, 52, 79} can be involved in either condition. The elevated globulin in both periarteritis nodosa and sarcoidosis has been mentioned already.

It is true that bone involvement (in approximately 15 per cent of the cases) and uveal tract and parotid gland involvement (20 per cent) occur in sarcoidosis and have not been reported in periarteritis nodosa, as yet.

It can be stated, therefore, that most organs can be involved in either condition, even if some organs are more frequently involved in periarteritis nodosa and others in sarcoidosis. Here again the different stages of the evolution of the disease have to be taken into consideration.

Finally, both conditions respond to ACTH and/or cortisone.^{3, 20, 25, 54, 61, 88} Ehrlich²³ states that the so-called collagen diseases would be more properly designated as dysgamma-globulinemias, because the common denominator of the various collagen diseases lies in the pathogenesis, in the production of abnormal gamma globulin by plasma cells (due to antibodies) causing injury of the general mesenchyme. The same is also true in the case of sarcoidosis.

The hypersensitivity agent (whatever it may be) causes in susceptible persons an antigen antibody reaction with increase in the gamma globulin, eosinophils, plasma cells and lymphocytes. It is known that the function of the eosinophil is related to abnormal protein; antibodies are chemotactic for the eosinophil. They produce a localized eosinophilia at the site of the antigen invasion and, if more eosinophils are produced, there is an invasion by the eosinophil into the blood stream.

The connective tissue is not stable but in a labile state of constant changes under control of opposing hormonal forces. Under stress conditions the organism attempts to reestablish homeostasis by increased ACTH production, decrease of the eosinophils, plasma cells, lymphocytes, inhibition of fibroblast proliferation, suppression of membrane permeability, etc. If the noxious stimulus lasts long enough and is strong enough—as in allergic states—there will be a hormonal imbalance, with proliferation of the connective tissue and granuloma formation. Selye^{85, 86, 87} has shown that DCA stimulates granuloma formation, fibroblast production, increases deposition of collagen and enhances the permeability of the synovial membrane, while cortisone acts in the opposite direction by inhibiting fibroblast proliferation and suppressing membrane permeability.

Clearly the so-called collagenous diseases are a heterogeneous group necessitating reclassification. Recently chronic relapsing nonsuppurative panniculitis (Christian-Weber disease) has been classified under collagen diseases.¹¹ Nosology on the basis of the system involved is not sufficient—we will not classify hypernephroma and renal tuberculosis as the same dis-

case just because the same organ is involved—but common etiology, similarity in the histologic, biochemical and clinical picture, and common therapeutic response to ACTH and cortisone could be a criterion for classification.

It is probable that there are no such separate entities as periarteritis nodosa and sarcoidosis, but that both—perhaps together with serum sickness—should be classified as hypersensitivity granulomas, vascular or extravascular, acute or chronic.

SUMMARY AND CONCLUSIONS

Five proved cases of periarteritis nodosa and one of sarcoidosis are described.

The similarities of the etiologic, clinical, biochemical, histologic and therapeutic aspects of both entities are discussed.

It is considered very likely that periarteritis nodosa and sarcoidosis are not two distinct and separate entities but constitute different stages of the same disease entity. This entity should be labeled "hypersensitivity granuloma," acute or chronic, perivascular or extravascular.

The so-called collagen diseases are a heterogeneous group requiring a more concise classification.

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BIBLIOGRAPHY

1. Adelson, L.: Periarteritis nodosa in infancy, *J. Pediat.* **39**: 346, 1951.
2. Arkin, A.: Clinical and pathological study of periarteritis nodosa, *Am. J. Path.* **6**: 401, 1930.
3. Baggenstoss, A. H., Shick, R. M., and Polley, H. F.: Effect of cortisone on lesions of periarteritis nodosa, *Am. J. Path.* **27**: 537, 1951.
4. Baker, L. A.: Periarteritis nodosa with report of two cases, *Ann. Int. Med.* **17**: 223, 1942.
5. Banks, B. M.: Is there a common denominator in scleroderma, dermatomyositis, disseminated lupus erythematosus, Libman-Sacks syndrome and polyarteritis nodosa? *New England J. Med.* **225**: 433, 1941.
6. Barnum, D. R., de Takats, G., and Delkart, R. E.: Periarteritis nodosa following thiouracil therapy of hyperthyroidism, *Angiology* **2**: 256, 1951.
7. Bergstrand, H.: Morphological equivalents in polyarthritis rheumatica, periarteritis nodosa, etc., *J. Path. and Bact.* **58**: 399, 1946.
8. Berne, R. M.: An unusual sensitivity reaction to penicillin: report of a case with autopsy findings, *New England J. Med.* **242**: 814, 1950.
9. Boyd, L. J.: Periarteritis nodosa, abdominal manifestations, *Bull. New York M. Coll., Flower and Fifth Ave. Hosps.* **4**: 27, 1941.
10. Boyd, L. J.: Pulmonary manifestations of periarteritis nodosa, *Bull. New York M. Coll., Flower and Fifth Ave. Hosps.* **7**: 94, 1944.
11. Brudno, J. C.: Chronic relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian disease), *New England J. Med.* **243**: 513, 1950.
12. Case records of the Massachusetts General Hospital (Case 36381), *New England J. Med.* **243**: 454, 1950.

13. Case records of the Massachusetts General Hospital (Case 37511), New England J. Med. **245**: 978, 1951.
14. Churg, J., and Strauss, L.: Allergic granulomatosis, allergic angiitis and periarteritis nodosa, Am. J. Path. **27**: 277, 1951.
15. Contratto, A. W.: Periarteritis nodosa: a report of two cases, one with special reference to sensitivity factors, Arch. Int. Med. **80**: 567, 1947.
16. Current Comment: Saranac symposium on the beryllium problem, J. A. M. A. **137**: 648, 1948.
17. Curtis, A. C., and Grekin, R. H.: Sarcoidosis. III. A review, M. Clin. North America **33**: 31, 1949.
18. Curtis, G. H.: Cutaneous hypersensitivity due to beryllium: a study of 13 cases, Arch. Dermat. and Syph. **64**: 470, 1951.
19. Diaz-Rivera, R. S., and Miller, A. J.: Periarteritis nodosa, a clinicopathologic analysis, Ann. Int. Med. **24**: 420, 1946.
20. Downing, J. G.: The use of ACTH and cortisone in dermatology, New England J. Med. **246**: 56, 1952.
21. Dupont, A.: Un cas de bouton d'orient à structure de sarcoïde de Boeck, Ann. de dermat. et syph. **1**: 453, 1930.
22. Eason, J., and Carpenter, G.: Treatment of acute rheumatic polyarthritis with concentrated antiscarlatinal serum, Quart. J. Med. **30**: 93, 1937.
23. Ehrich, W. E.: Nature of collagen diseases, Am. Heart J. **43**: 121, 1952.
24. Finkelstein, W., and Brewnan, P. J.: Periarteritis nodosa, brief review and case report, Connecticut M. J. **7**: 104, 1943.
25. Forsham, P. H.: Present status of ACTH and cortisone in therapy, M. Clin. North America **35**: 1229, 1951.
26. Frazier, C. N., and Hu, C. K.: Isolation of *Treponema pallidum* from subcutaneous sarcoid, Proc. Soc. Exper. Biol. and Med. **30**: 898, 1933.
27. Freiman, D. G.: Sarcoidosis, New England J. Med. **239**: 664-671, 709-716, 743-749, 1948.
28. Friedberg, C. K., and Gross, L.: Periarteritis nodosa (necrotizing arteritis) associated with rheumatic heart disease, Arch. Int. Med. **54**: 170, 1934.
29. Gartside, I. B.: Granulomatous arteritis in lesions resembling sarcoidosis, J. Path. and Bact. **56**: 61, 1944.
30. Gelfand, M. L., and Aronoff, S.: Periarteritis nodosa; possible relation to the increased usage of sulfonamides, Ann. Int. Med. **30**: 919, 1949.
31. German, W. M.: Lupoid-sarcoid induced by foreign body (silica), Am. J. Clin. Path. **10**: 254, 1940.
32. Goodman, M. J.: Periarteritis nodosa with recovery: report of an unusual case apparently due to sensitivity to sulfadiazine, Ann. Int. Med. **28**: 181, 1948.
33. Gruber, G. B.: Zur Frage der Periarteritis nodosa, mit besonder Berücksichtigung der Gallenblasen und Nieren-Beteiligung, Virchows Arch. f. path. Anat. **247**: 294, 1923.
34. Gruber, G. B.: Zur Frage der Periarteritis nodosa, Virchows Arch. f. path. Anat. **258**: 441, 1925.
35. Harkavy, J.: Vascular allergy, III, J. Allergy **14**: 507, 1942-43.
36. Harris, W. A., Lynch, G. W., and O'Hare, J. P.: Periarteritis nodosa, Arch. Int. Med. **63**: 1163, 1939.
37. Harris, W. H.: Etiology and pathology of periarteritis nodosa, South. M. J. **19**: 426, 1926.
38. Harrell, G. T., and Horne, S. F.: The reaction to Lepromin of patients with sarcoid or tuberculosis compared with that of patients in general hospital with a discussion of the mechanism of the reaction, Am. J. Trop. Med. **25**: 523, 1945.
39. Helperin, M., and Trubek, M.: Necrotizing arteritis and subacute glomerulonephritis in gonococcus endocarditis. Toxic origin of periarteritis nodosa, Arch. Path. **15**: 35, 1933.

40. Hermann, W.: Pulmonary changes in a case of periarteritis nodosa, *Am. J. Roentgenol.* **29**: 607, 1933.
41. Hopps, H. C., and Wissler, R. W.: The experimental demonstration of generalized arteritis and periarteritis (periarteritis nodosa), *J. Lab. and Clin. Med.* **31**: 939, 1946.
42. Johnson, C. C., Hanson, N. O., and Good, C. A.: Erythema nodosum: the possible significance of associated pulmonary hilar adenopathy, *Ann. Int. Med.* **34**: 983, 1951.
43. Jones, G. M., Jr.: Periarteritis nodosa with case reports, *Ann. Int. Med.* **16**: 920, 1942.
44. Ketron, L. W., and Bernstein, J. C.: Cutaneous manifestations of periarteritis nodosa, *Arch. Dermat. and Syph.* **40**: 929, 1939.
45. King, B. G.: The clinical diagnosis of periarteritis nodosa: report of 4 cases, *Ann. Int. Med.* **32**: 466, 1950.
46. King, C. O.: Post traumatic sarcoid-like lesions, *South. M. J.* **39**: 122, 1946.
47. Kipkie, G. F.: Possible role of infection in the production of periarteritis nodosa in hypertensive rabbits, *Arch. Path.* **50**: 98, 1950.
48. Kipkie, G. F., and Johnson, D. S.: Possible pathogenic mechanisms responsible for human periarteritis nodosa: as suggested by the occurrence of two instances of this disease in association with glomerulonephritis, *Arch. Path.* **51**: 387, 1951.
49. Kissmeyer, A.: *La maladie de Boeck: Sarcoïdes cutanées benignes multiples*, 1932, Masson et Cie, Paris, p. 147.
50. Klein, S. P.: Periarteritis nodosa, *Arch. Int. Med.* **54**: 983, 1949.
51. Klemperer, P., Pollock, A. D., and Baehr, G.: Diffuse collagen disease, *J. A. M. A.* **119**: 331, 1942.
52. Klinefelter, H. F., Jr., and Salley, S. M.: Sarcoidosis simulating glomerulonephritis, *Bull. Johns Hopkins Hosp.* **79**: 333, 1946.
53. Kussmaul, A., and Meier, R.: Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, *Deutsch. Arch. f. klin. Med.* **1**: 484, 1866.
54. Levin, M. H., Adams, W. S., Beck, W. S., and others: Prolonged treatment of cases of periarteritis nodosa with ACTH: effective dose as measured by metabolic balances, *J. Clin. Endocrinol.* **11**: 343, 1951.
55. Lichenstein, L., and Fox, L. J.: Necrotizing arterial lesions resembling those of periarteritis nodosa and focal visceral necrosis following administration of sulfathiazole: report of a case, *Am. J. Path.* **22**: 665, 1946.
56. Logue, R. B., and Mullins, F.: Polyarteritis nodosa. Report of 11 cases with review of recent literature, *Ann. Int. Med.* **24**: 11, 1946.
57. McCormick, R. V.: Periarteritis occurring during propylthiouracil therapy, *J. A. M. A.* **144**: 1453, 1950.
58. Matsugi, M., and Sato, Y.: Über die allergisch Gewebsreaktion der Niere. Zugleich ein experimenteller Beitrag zur pathogenese der diffusen Glomerulonephritis und der Periarteritis nodosa, *Virchows Arch. f. path. Anat.* **293**: 615, 1934.
59. Middleton, W. S., and McCarter, J. S.: The diagnosis of periarteritis nodosa, *Am. J. M. Sc.* **190**: 291, 1945.
60. Motley, L.: Periarteritis nodosa with report of case showing unusual features and apparent recovery, *J. A. M. A.* **106**: 898, 1936.
61. Mundy, W. L., Walker, W. G., Jr., Rickerman, H. A., and Beck, G. J.: Periarteritis nodosa, report of a case treated with ACTH and cortisone, *Am. J. Med.* **11**: 630, 1951.
62. Old, J. W., and Russell, W. D.: Necrotizing pulmonary arteritis occurring with congenital heart disease (Eisenmenger complex): report of a case with necropsy, *Am. J. Path.* **26**: 789, 1950.
63. Ophuls, W.: Periarteritis acute nodosa, *Arch. Int. Med.* **32**: 870, 1923.
64. Otani, S.: Zur Frage nach dem Wesen der sog. Periarteritis nodosa, *Frankfurt. Ztschr. f. Path.* **30**: 208, 1924.

65. Pagel, W.: Polyarteritis nodosa and "rheumatic" disease, *J. Clin. Path.* **4**: 137, 1951.
66. Parker, F., Jr., and Weiss, S.: The nature and significance of the structural changes in the lungs in mitral stenosis, *Am. J. Path.* **12**: 573, 1936.
67. Pinner, M.: On etiology of sarcoidosis, *Am. Rev. Tuberc.* **54**: 582, 1946.
68. Prouty, M., and Shafer, E. L.: Periarteritis nodosa associated with ratbite fever due to *Streptobacillus moniliformis*, *J. Pediat.* **36**: 605, 1950.
69. Reiman, H. A., Price, A. H., and Hubut, P. A.: Trichinosis and periarteritis nodosa, differential diagnosis, possible relationship, *J. A. M. A.* **122**: 274, 1943.
70. Rich, A., and Gregory, J. E.: Experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity, *Bull. Johns Hopkins Hosp.* **72**: 65, 1943.
71. Rich, A. R.: The role of hypersensitivity in periarteritis nodosa, *Bull. Johns Hopkins Hosp.* **71**: 123, 1942.
72. Rich, A. R.: Additional evidence of role of hypersensitivity in etiology of periarteritis nodosa, *Bull. Johns Hopkins Hosp.* **71**: 375, 1942.
73. Rich, A. R.: Hypersensitivity to iodine as a cause of periarteritis nodosa, *Bull. Johns Hopkins Hosp.* **77**: 43, 1945.
74. Rich, A. R.: Hypersensitivity in disease with especial reference to periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus and rheumatoid arthritis in Harvey Lectures, 1946-1947, The Science Press Printing Co., Lancaster, Pa., p. 106.
75. Riley, E. A.: Boeck's sarcoid: a review based upon a clinical study of 52 cases, *Am. Rev. Tuberc.* **62**: 231, 1950.
76. Rose, M. H., Litmann, D., and Houghton, J.: Polyarteritis nodosa, a clinical and pathological study and report of 6 cases, *Ann. Int. Med.* **32**: 1114, 1950.
77. Rosenberg, A., Jr.: Etiologic and immunologic concepts regarding sarcoidosis, *Arch. Dermat. and Syph.* **64**: 385, 1951.
78. Rosenthal, S. R.: Pathological and experimental studies of Boeck's sarcoid, *Am. Rev. Tuberc.* **60**: 236, 1949.
79. Rotenberg, L., and Guggenheim, A.: Boeck's sarcoid: report of a case with renal involvement, *Dis. of Chest.* **8**: 392, 1946.
80. Rubin, E. H., and Pinner, M.: Sarcoidosis, *Am. Rev. Tuberc.* **49**: 146, 1944.
81. Rubin, E. H.: Diseases of the chest, 1947, W. B. Saunders Co., Philadelphia, p. 310.
82. Sandler, B. P., Matthews, J. H., and Bornstein, S.: Pulmonary cavitation due to polyarteritis, *J. A. M. A.* **144**: 754, 1950.
83. Selye, H.: Hormonal production of arthritis, *J. A. M. A.* **114**: 201, 1944.
84. Selye, H., and Pentz, E. I.: Pathological correlation between periarteritis nodosa, renal hypertension and rheumatic lesion, *Canad. M. A. J.* **49**: 264, 1943.
85. Selye, H.: General adaptations syndrome and disease of adaptation, *J. Allergy* **17**: 358, 1946.
86. Selye, H.: Role of somatotrophic hormone in production of malignant nephrosclerosis, periarteritis nodosa, and hypertensive disease, *Brit. M. J.* **1**: 263, 1951.
87. Selye, H.: The general adaptation syndrome and the disease of adaptation, *J. Clin. Endocrinol.* **6**: 117, 1946.
88. Shick, R. M., Baggenstoss, A. H., Fuller, B. F., and Polley, H. F.: Effects of cortisone and ACTH on periarteritis nodosa and cranial arteritis, *Proc. Staff Meet., Mayo Clin.* **25**: 135, 1950.
89. Silverman, J. J., and Worthen, J. F.: Agranulocytosis in a patient treated with mercurial diuretics, *J. A. M. A.* **148**: 200, 1952.
90. Slinger, W. N., and Starck, V.: Cutaneous form of polyarteritis nodosa, *Arch. Dermat. and Syph.* **63**: 641, 1951.
91. Solomon, S., Kasich, M., and Kiven, N.: Periarteritis nodosa with report of three cases diagnosed during life, *Ann. Int. Med.* **21**: 638, 1944.
92. Staehelin, H. R.: Zur Frage der Besnier-Boeck'schen Krankheit und der Periarteritis nodosa, *Virchows Arch. f. path. Anat.* **309**: 235, 1942.

93. Sweeney, A. R., Jr., and Baggenstoss, A. H.: Pulmonary lesions of periarteritis nodosa, Proc. Staff Meet., Mayo Clin. **24**: 35, 1949.
94. Symmers, W. St. C., and Gillett, R.: Polyarteritis nodosa associated with malignant hypertension, disseminated platelet thrombosis, "wire loop" glomeruli, pulmonary silicotuberculosis and sarcoidosis-like lymphadenopathy, Arch. Path. **52**: 489, 1951.
95. Teilum, G.: Allergic hyperglobulinosis and hyalinosis (paramyloidosis) in reticuloendothelial system in Boeck's sarcoid and other conditions: morphologic immunity reaction, Am. J. Path. **24**: 389, 1948.
96. Teilum, G.: Pathogenetic studies on lupus erythematosus disseminatus and related diseases, Acta med. Scandinav. **123**: 126-142, 1946.
97. Thorn, G. W., Renold, A. E., Wilson, D., Frawley, T. F., Jenkins, D., Gracia-Heyes, J., and Forsham, P. H.: Clinical studies on the activity of orally administered cortisone, New England J. Med. **245**: 549, 1951.
98. Ureles, A. L., and Kalmansohn, R. B.: Oral administration of cortisone in a case of erythema nodosum, New England J. Med. **245**: 139, 1951.
99. Vance, B. M., and Graham, J. E.: Periarteritis nodosa complicated by fatal intrapericardial hemorrhage, Arch. Path. **12**: 521, 1931.
100. Van Ordstrand, H. S.: Current concepts of beryllium poisoning, Ann. Int. Med. **35**: 1203, 1951.
101. Van Wyk, J. J., and Hoffman, C. R.: Periarteritis nodosa, a case of fatal exfoliative dermatitis resulting from "dilantin sodium" sensitization, Arch. Int. Med. **81**: 605, 1948.
102. Vining, C. W.: A case of periarteritis nodosa with subcutaneous lesions and recovery, Arch. Dis. Childhood **13**: 31, 1938.
103. Wechsler, Q. S., and Bender, M. D.: Neurologic manifestations of periarteritis nodosa, J. Mt. Sinai Hosp. **8**: 1071, 1942.
104. Wegener, F.: Über generalisierte septische Gefässerkrankungen, Verhandl. d. deutsch. path. Gesellsch. **29**: 202, 1936.
105. Weiss, S.: Disease associated with inflammatory lesions of the peripheral arteries, New England J. Med. **225**: 579, 1941.
106. Weinberg, T.: Granulomas of unknown etiology associated with periarteritis nodosa, Am. J. Path. **22**: 645, 1946.
107. Wilens, S. L., and Glynn, J.: Hypertensive and non-hypertensive periarteritis nodosa, Arch. Int. Med. **88**: 51, 1951.
108. Wilson, K. S., and Alexander, H. L.: Relation of periarteritis nodosa to bronchial asthma and other forms of human sensitiveness, J. Lab. and Clin. Med. **30**: 195, 1945.
109. Wold, L. E., and Baggenstoss, A. H.: Gastro-intestinal lesions of periarteritis nodosa, Proc. Staff Meet., Mayo Clin. **24**: 28, 1949.
110. Zeek, P. M., Smith, C. C., and Weeter, J. C.: Studies on periarteritis nodosa. III. The differentiation between vascular lesions of periarteritis nodosa and of hypersensitivity, Am. J. Path. **24**: 889, 1948.

CASE REPORTS

BERYLLIUM GRANULOMATOSIS COMPLICATED BY TUBERCULOSIS: REPORT OF A CASE TREATED WITH ACTH *

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ALTHOUGH beryllium and its compounds have been recognized as serious industrial hazards for only a decade, the available information concerning toxic manifestations in man and experimental animals has already become extensive. The first patient with a diffuse pulmonary granulomatosis later shown to have been due to beryllium was observed during 1941 at the Essex Sanatorium in Middleton, Massachusetts.¹ Following recognition of the clinical entity, many controversies arose concerning the rôle of beryllium as an etiologic agent as opposed to that of the electronegative ions of beryllium salts. The experimental investigation of poisoning due to this metal has been characterized by apparently contradictory findings from studies of compounds or metal in various physical states and in different animal species.^{2, 3} It can now be said with a degree of certainty, however, that beryllium in various forms, especially as a fume or as the oxide, and also in its various metallic salts, can induce two principal types of disorder involving the respiratory system. The first is an acute pneumonitis,⁴ usually transient in character, and only rarely followed by development of a chronic and more serious type of lesion. The second is a grave chronic pulmonary disease, characterized by progressive and extensive granulomatosis. The essential lesion strongly resembles that of Boeck's sarcoid and is frequently mistaken for this disease, since months and more frequently years may elapse between the initial exposure to beryllium and the development of recognizable disease. The complete clinical spectrum of this chronic disease is not yet known. It is now commonly believed, however, that in at least a third of the instances there is progression with increasing dyspnea and respiratory handicap, leading ultimately to death from hypoxia.

There have been many excellent compilations of clinical data,^{5, 6, 7, 8} as well as studies of the pathology of the disease.^{9, 10} In many respects the case reported was found, in retrospect, to follow the pattern of chronic beryllium granulomatosis. There are several features of special interest, however, which add to our understanding of the possible complications of the disease and the difficulties of therapeutic management.

CASE REPORT

The patient, a 37 year old scientist, was well until the summer of 1945. He then noted gradual development of shortness of breath and easy fatigability, accompanied by a dry, paroxysmal, nonproductive cough. The symptoms progressed until he had

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marked dyspnea on climbing one flight of stairs. There was a weight loss of 20 pounds in the course of a few months. Chest radiographs made in October and November, 1945, showed a diffuse, fine mottling throughout both lung fields (figure 1). A routine chest film taken at his place of employment just five months previously had been negative (figure 2). He was seen by a physician in November, 1945. The past history and family history were essentially negative. The following clinical data were obtained:

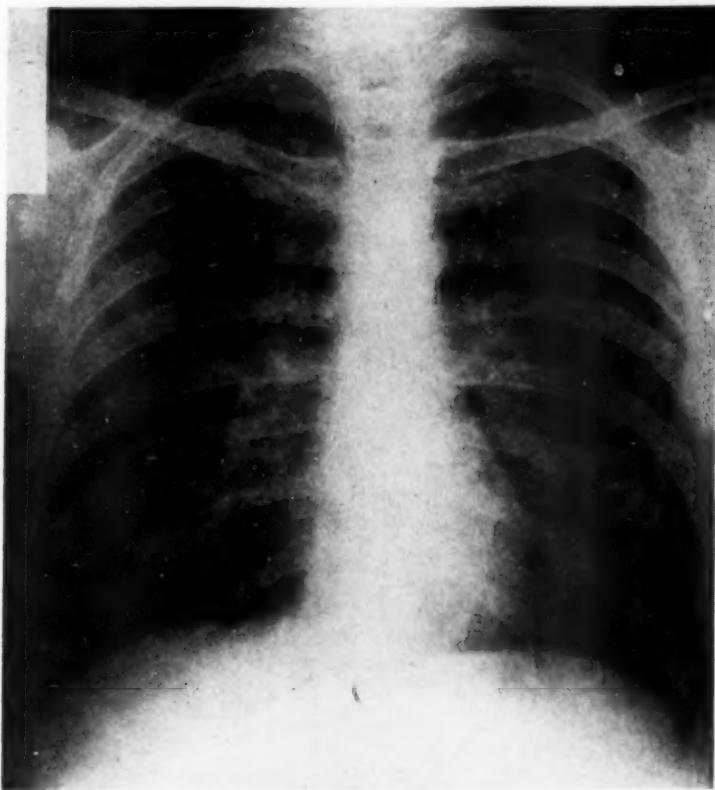


FIG. 1. The first abnormal radiograph, taken in October, 1945, showing widespread mottling.

Occupational History: Following his college training, the patient worked as a physicist at atomic energy development projects between 1941 and the discovery of his disease in 1945. During this period he did not receive significant radiation exposure. He worked with electromagnetic separators and used a number of different elements—thallium, mercury, lead and uranium. He recalled having had inhalation exposures to uranium oxide, uranium tetrachloride, uranium hexafluoride, uranium metal, finely divided carbon, hydrochloric acid, fluorine, and possibly small amounts of phosgene gas.

Physical Examination: The patient was a tall, underweight 31 year old male showing evidence of recent weight loss. He was afebrile; pulse, 90; respirations, 20; blood pressure, 130/100 mm. of Hg. There was faint cyanosis of the nail beds and lips and slight pallor of the skin but no clubbing of the fingers. A small lymph node was felt in the left supraclavicular fossa, and one at the anterior edge of the trapezius muscle on the right. The thorax was long, with a narrow A-P diameter, and expanded symmetrically 4 inches. The clavicles were held in an elevated position. The supraclavicular and infraclavicular fossae were retracted. There was

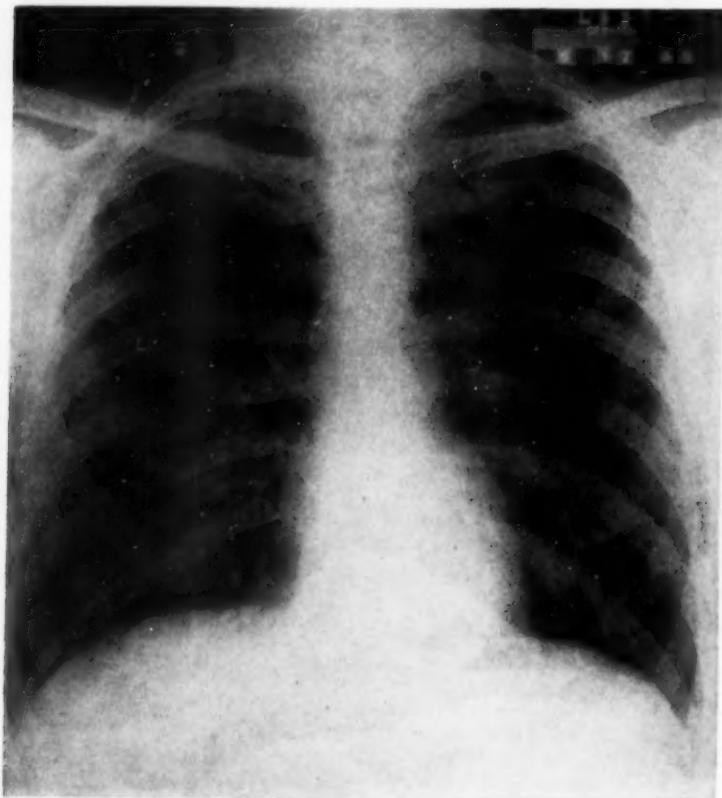


FIG. 2. Normal radiograph, taken five months previous to that shown in figure 1.

no abnormal fremitus; resonance was slightly impaired bilaterally. Breath sounds were roughened on both sides posteriorly and over the right upper chest anteriorly. The expiratory phase was prolonged. Inconstant fine rales, which persisted after coughing, were heard at both apices and at the right base. There were no abnormal cardiac findings. The liver was palpable at the right costal margin and in the midline 3 cm. below the xiphoid; it was nontender and firm. The upper border was thought to be at the level of the seventh intercostal space. The remainder of the examination was negative.

The vital capacity was 4.5 L. X-ray studies of the hands and feet were normal. A slit lamp examination showed no uveitis or other abnormality.

Course: The patient was admitted to the hospital on January 4, 1946, for further study.*

Blood counts were normal except for a leukopenia of 3,500, with normal differential. (Routine blood counts done prior to his entry had shown a mild leukopenia during the past three months.) A Wintrobe sedimentation rate was 25 mm. per hour. The vital capacity was 3.8 L. Urologic studies, including urinalysis, Mosenthal concentration test, urea clearance and intravenous pyelograms, were normal. Tuberculin and coccidioidin skin tests were negative. Serologic tests for undulant fever, tularemia, typhoid, paratyphoid A & B and psittacosis were also negative. The sternal marrow appeared normal. A lymph node biopsy from the right inguinal region on January 9, 1946 was normal. A cervical lymph node was removed on January 17, 1946. Microscopic examination revealed small scattered granulomata (figure 3), which were considered to be compatible with Boeck's sarcoid or tuberculosis. At the time of his discharge from the hospital the diagnosis of his disease was not clear. Sarcoidosis, toxicity from radioactive materials, pulmonary tuberculosis and pneumoconiosis were being considered.

After he left the hospital his status changed very little except that the persistent irritative cough became productive of small amounts of yellow mucoid sputum. Coughing produced soreness in the throat and anterior chest pain. Occasionally exertion caused dull precordial pain, which rapidly subsided with rest. Repeated chest films showed no further changes. Serologic tests for infection with *Coccidioides immitis* were negative.

The patient reentered the hospital on February 17, 1947, because of microscopic hematuria. Findings on physical examination were essentially unchanged. The previously observed leukopenia had disappeared. The Wintrobe sedimentation rate was now 8 mm. per hour. Microscopic examination of the urine showed a few red blood cells and occasional granular casts. Mosenthal concentration and phenol-sulfonphthalein tests were normal; a few days later an Addis count was also normal. An intravenous pyelogram failed to reveal evidence of disease. Extensive immunologic studies were again negative. The vital capacity was now only 1.8 L. Repeated sputum studies for tuberculosis and investigations for fungi were negative. X-ray studies of the lungs showed no visible change in the disease process, and the hands again appeared normal.

When the patient was discharged from the hospital on February 25, 1947, an etiologic diagnosis was still wanting. However, he was thought to have chronic diffuse interstitial fibrosis of the lungs with emphysema of undetermined etiology. The cause of the hematuria was not clear, but it was thought to be due to renal embolus from a pulmonary vein thrombosis.

During the two year period following the second hospitalization, from February, 1947, until December, 1948, the patient's condition changed little, although dyspnea slowly increased and became noticeable at rest. There was no further weight loss. Occasional nocturnal cough produced a small amount of yellow sputum without blood streaking. A blood count in August, 1948, showed 18 gm. hemoglobin, 6.28 million erythrocytes and 14,000 leukocytes. He continued his scientific work at the laboratory. Late in 1947, radiographs of the chest revealed small bilateral pneumothoraces, and there was an increase in the density of the hilar shadows. Radiographs made during 1948 showed slight change in the size and shape of the localized pneumothoraces, but the parenchymal shadows remained for the most part the same (figure 4). Early in December, 1948, the vital capacity was 1.7 L.

On December 12, 1948, while at rest, the patient developed a sudden severe pain

* We are indebted to Dr. S. P. Lucia for the results of the hospital studies.



FIG. 3. Granuloma in cervical lymph node biopsy, January, 1946 ($\times 300$).

in the left chest and marked dyspnea. When he entered the hospital on the same day he was in distress, dyspneic and cyanotic. He had tachycardia and was febrile. The classic signs of pneumothorax were noted on the left, and this diagnosis was substantiated by x-ray examination. The patient improved with oxygen therapy, and the lung slowly reexpanded.

On December 23, 1948, he was transferred by ambulance to the chest service of another hospital, where he remained for sanatorium care until May 14, 1949.*

* During this and his next hospitalization, as well as the intervening period, the patient was under the continuous care of Dr. Seymour M. Farber and Dr. Judith Smith, to whom we are indebted for the results of hospital studies.

Shortly after he left the hospital he was well enough to continue part-time work. Although very dyspneic after mild exertion, he was able to live fairly comfortably within the limits imposed by his disease. That year he was included among a number of patients whose lung ventilation patterns were studied by Robertson et al.¹¹ by a method of mass spectrometric determination of nitrogen elimination rates. His ventilation efficiency was the lowest found, being 0.06, compared to the normal mean of 0.57. The mean value of a group of 12 patients with lung pathology was 0.31.

There was little apparent change in his condition for almost a year. On March 8, 1950, while resting, he coughed up about 50 c.c. of bright red blood. No signs or other symptoms accompanied this episode, and he was kept at bed-rest. A chest radiograph on March 13, 1950 showed some increase in density of the upper left lung field; otherwise the appearance was little changed, except for disappearance of the apical pneumothoraces.

Final Hospitalization: He was readmitted to the hospital on March 23, 1950, because his condition in general seemed to be deteriorating.

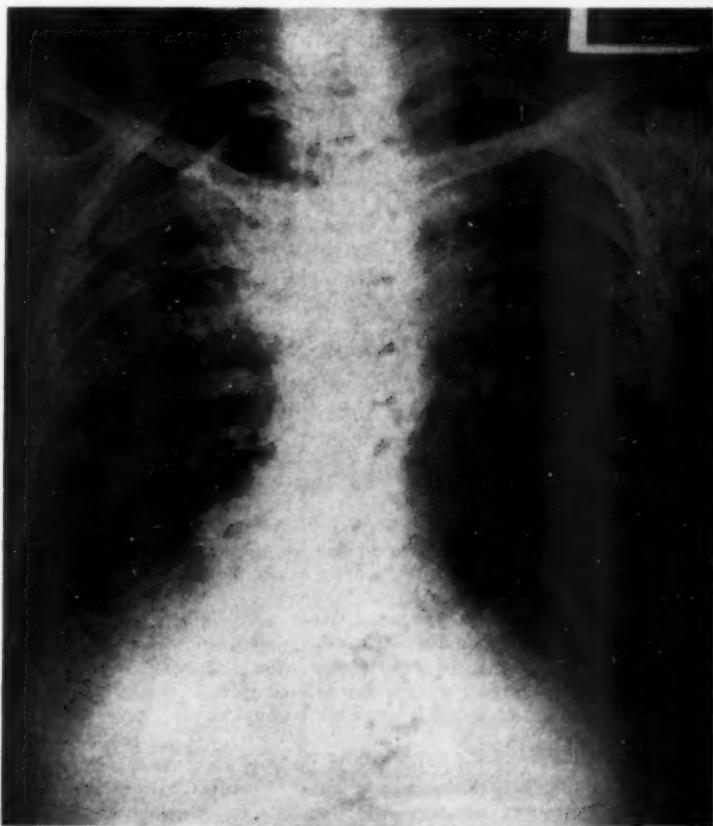


FIG. 4. Radiograph taken in September, 1948, showing increased mediastinal shadow and apical pneumothorax.

On admission his temperature was 102.2° F.; pulse, 100; respirations, 32; blood pressure, 110/70 mm. of Hg. He was dyspneic and cyanotic at rest and appeared gravely ill. Dyspnea was only moderately improved by oxygen therapy. There was no palpable lymphadenopathy. Respiratory movements of the thorax were limited. The bases were hyperresonant. Throughout the lung fields there were inspiratory and expiratory râles and rhonchi. The fingernails were long and curved anteriorly; they appeared slightly cyanotic. True clubbing was not present.

His blood count showed 14.1 gm. hemoglobin, 4.75 million erythrocytes, 14,700 leukocytes, with 54 per cent neutrophils, 12 per cent nonfilamented neutrophils, 30 per cent lymphocytes, 3 per cent monocytes and 1 per cent basophils.

The diagnosis at this time was diffuse pulmonary fibrosis—etiology unknown, but probably beryllium—emphysema, hemoptysis and superimposed pulmonary infection, probably tuberculosis.

Two days after admission the patient had a massive hemoptysis of about 700 c.c. He was given trials of penicillin, aureomycin and streptomycin, none of which had any apparent effect on his stormy febrile course. Continuous oxygen therapy was given. Because tuberculosis seemed likely, streptomycin was continued and para-aminosalicylic acid administration was initiated.

On April 3, 1950, acid-fast bacilli were found in the patient's sputum.

In response to further questioning, the patient finally recalled a beryllium exposure. In the spring of 1942 the group with whom he was working had occasion to use beryllium ceramics which they fabricated themselves. The patient did not recall having made any of these, but remembered specifically having used a power drill on several occasions to make holes in a beryllium oxide crucible. He recalled that during this process dust was formed by the drill, which he inhaled while doing close work. Confirmation was obtained by reference to laboratory notebooks. It is of interest to note that the patient had been repeatedly questioned by several physicians throughout his long illness regarding possible exposure to beryllium. Until this time, in April, 1950, neither he nor persons under whose direction he had worked recalled the exposure.

A spiking febrile course continued. By the end of his third week in the hospital he was moribund.

Cortisone therapy was started on the twenty-first hospital day; 100 mg. were given intramuscularly three times each day. Streptomycin was continued. During the first three days of cortisone treatment there was some subjective improvement and a gradual decline of the fever (figure 5). This was followed by a relapse, and ACTH was substituted for the cortisone. This was given in 25 mg. doses four times a day. The response was dramatic. The temperature and pulse immediately fell to normal and the patient's clinical condition was markedly improved. During the next few weeks his pulmonary physical findings improved, and he was able to be out of the oxygen tent for two or three hours a day without becoming cyanotic. His vital capacity was 2.2 L.

Thirty-three days after ACTH was started, and while the patient was continuously treated with streptomycin and para-aminosalicylic acid, sputum cultures and guinea pig inoculation tests were positive for acid-fast bacilli. No further sputum samples were obtained during the next four and one-half months. Two samples examined by smear during his seventh hospital month, however, were negative.

Following the initial response to ACTH therapy, the patient's condition failed to improve noticeably during the next six months. However, x-ray shadows ascribed to tuberculosis in the upper left lung field showed some clearing, and râles cleared completely from his chest. On one occasion the dose of ACTH was reduced to 25 mg. for one day. By the following morning his temperature had spiked to 103° F.,

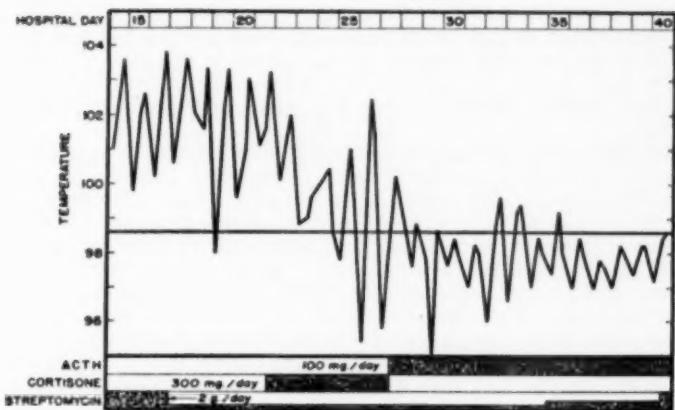


FIG. 5. Initial temperature response to cortisone and then to ACTH.

and he had a chill (figure 6). There was an increase in moisture in the lungs and his clinical condition became worse. The dose of ACTH was again increased and the patient promptly returned to his previous status. On another occasion ACTH was omitted for two days because the drug was temporarily unavailable. A similar relapse occurred (figure 7). Prompt improvement followed reinstitution of the hormone.

Ancillary treatment consisted of a low sodium, high potassium diet, calcium lactate, potassium chloride, ascorbic acid and thyroid substance by mouth. The patient gradually developed a "moon face" and deposited a considerable amount of adipose tissue in the abdominal wall. There was acne over the trunk. Hypertension, abdominal striae and edema did not appear. The excretion of 17-ketosteroids was elevated to 41 mg. per 24 hours one month after ACTH was started. Subsequent

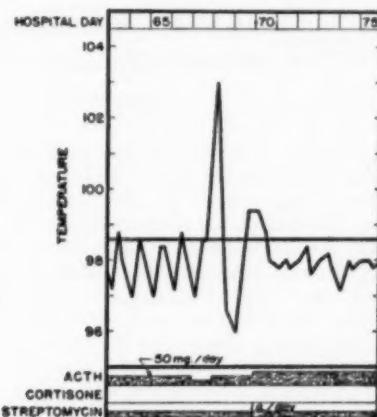


FIG. 6. Febrile response to decrease in ACTH dosage.

determinations showed gradually decreasing values; after six months of ACTH therapy the value was 16.5 mg. per 24 hours. Eosinophils, which had been suppressed, reappeared in the peripheral blood at the same time: in two 500 cell counts, three eosinophils were seen. No appreciable alteration of the fasting blood sugar was noted, but the hormone therapy resulted in a typical prolonged type of glucose tolerance curve.

In the fifth month of hospitalization the patient developed herpes zoster along the sensory branch of the common peroneal nerve of the left leg. In the seventh month streptomycin was discontinued for an unstated reason. For three days after this the patient was clinically worse; then he appeared to become stabilized again simultaneously with an increase of ACTH dosage from 50 to 60 mg. per day. During the eighth month a spontaneous pneumothorax occurred on the right side, resulting in extreme dyspnea and cyanosis. The patient's condition again became grave. Repeated withdrawal of air from the pleural space and continuous oxygen therapy resulted in some improvement. Radiograms of the chest showed reexpansion of the lung. However, his general downward course continued. At the end of eight months in the hospital, and after seven months of continuous ACTH therapy, the patient died in respiratory failure.

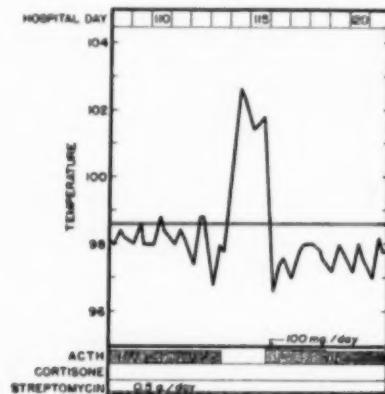


FIG. 7. Marked febrile response to temporary cessation of ACTH therapy.

*Autopsy.** The patient was fairly well developed but appeared thin and showed evidence of recent weight loss. Opening of the thorax revealed pleural thickening, with organized adhesions binding the surfaces of both lungs to the thoracic wall and to the diaphragm and mediastinal tissues obliterating the pleural space. The lungs were voluminous and had lost their elasticity. Their combined weight was 1,800 gm. The surfaces were irregular and nodular. The nodular regions varied from 1 to 3 cm. in diameter, were present in all lobes, and were of a rubbery consistency. On section the mottled grayish white nodules were fairly well circumscribed and surrounded by congested lung tissue. There were a number of cavities 1 to 3 cm. in diameter, with fibrous walls in both upper lobes. Some of the cavities contained cloudy exudate. Lymph nodes in the hilar regions and in the mediastinum were

*The authors are indebted to Dr. George A. Paxton for his considerable work with the autopsy material and for supplying the information from the postmortem examination.

enlarged. Some were fused, forming masses 2 and 3 cm. in diameter. On section, some of the nodes were of rubbery consistency and homogeneous gray color; others were firmer, with a grayish white fibrous appearance. All were heavily pigmented with carbon.

The pericardial cavity was normal and the cardiac surface smooth. The heart weighed 550 gm. There was moderate hypertrophy of the right ventricle, which measured 1.2 cm. in thickness. The right heart chambers were slightly dilated. There were small fibrotic thickened areas in the free margin of the mitral valve cusp and slight thickening of the chordae tendineae. The valves were otherwise normal.

Opening of the abdomen showed visceral relationships to be normal. The liver appeared slightly enlarged and weighed 1,750 gm. The spleen weighed 250 gm. and had a slightly increased consistency. On the cut surface the splenic pulp was firmer than normal. It had a brownish red color and somewhat glistening surface. The adrenals appeared enlarged, with the bulk of the enlargement in the medullary portion. No gross alterations in the cortex were noted. Their combined weight was 25 gm.

The thyroid appeared enlarged. No other significant findings were noted on gross examination.

Microscopically the lungs showed large masses of necrotic caseous material and dense fibrous connective tissue. Scattered multinucleated giant cells were seen in the perinecrotic inflammatory and fibrous connective tissue. There were small granulomas made up of epithelioid cells scattered throughout the lungs. A few fibroblasts, lymphocytes and plasma cells were present in these granulomatous foci. In a few older granulomatous lesions there was more connective tissue, with fewer epithelioid and chronic inflammatory cells. Some granulomas contained degenerating cellular debris and amorphous hyaline material. Alveolar septa were thickened and blood vessel walls were thickened and hyalinized. In many alveoli there were masses of acellular hyaline substance which in some cases had formed hyaline membranes covering the alveolar walls. In other areas the septa were ruptured, forming large emphysematous spaces. In several blood vessels masses of hematopoietic cells were seen forming emboli. Acid-fast stains revealed acid-fast organisms in all the lung and hilar node tissue in both the caseous and fibrotic areas.

On microscopic examination of the hilar nodes, most of the tissue was seen to consist of amorphous acellular masses of dense pink staining material, surrounded by narrow bands of lymphoid tissue containing numerous granulomas of the types described above. Langhans' giant cells were present in the granulomas. Scattered deposits of carbon pigment were present.

It was the pathologist's conclusion that the patient had subacute disseminated tuberculosis and that the following findings were probably results of berylliosis (clinical diagnosis): pulmonary fibrosis, cardiac hypertrophy, cor pulmonale, chronic passive congestion of the liver, and fatty metamorphosis of the liver with central lobular necrosis.

It should be pointed out here that a reexamination of the cervical lymph node removed in 1946 (figure 3) showed scattered throughout the lymphoid tissue small epithelioid granulomatous lesions composed of large pale staining epithelioid cells with rounded and ovoid nuclei and abundant pale eosinophilic cytoplasm. The follicular pattern and node architecture were fairly well preserved, although germinal centers were tiny or absent in most areas. A multinucleated giant cell of the Langhans type, with approximately 10 nuclei located peripherally, was present in one small granuloma. No necrosis was seen, and acid-fast staining revealed no tubercle bacilli.

Tissue Analyses for Beryllium: Tissue samples obtained at autopsy were analyzed

TABLE I
Beryllium Concentration in Micrograms per Gram Wet Tissue

Sample	Laboratory No. 1	Laboratory No. 2	Laboratory No. 3
Hilar lymph nodes	0.075	0.23	0.25
Lung	0.0096	0.026	0.002
Heart muscle	0.0000	0.0000	0.005
Liver	0.0000	0.0012	0.005
Thyroid	0.000	No sample	0.06
Spleen	0.000	No sample	0.15

for beryllium in three different laboratories.* While there was variation in the reported tissue concentrations of beryllium, as shown in table 1, the results indicate the presence of significant amounts which are many times higher than normal, and which fall into the range found in one of the laboratories in other cases of known beryllium exposure which were also fatal.¹²

COMMENT

In 1945 when this young scientist, engaged in research in a radiation laboratory, was found to have pulmonary disease, there was inadequate definitive knowledge of the toxicity of many of the substances to which he was exposed. The possibility that beryllium produced a serious lung disease was just beginning to be acknowledged in clinical reports.^{5, 6} It is not remarkable, therefore, that the orientation of the physicians who first attempted to make a diagnosis was toward the possibility of toxicity from radioactive materials, if the diagnosis of better understood diseases such as tuberculosis or sarcoidosis could not be established. In the course of time the likelihood of beryllium as an etiologic agent was given more weight, in view of the knowledge that this metal is widely used in radiation laboratories, and because the course of the disease was not characteristic of either Boeck's sarcoid or other known granulomatous lesions of the lung.

The difficulty of diagnosis frequently noted in this disease is impressively illustrated in this instance. Although the patient was unusually intelligent and thoroughly cooperative, and despite the fact that he was interviewed by a number of persons familiar with beryllium disease, the essential history of exposure was not obtained until five years after the onset of illness and eight years after the event. To understand the reason for the delay in establishing a sound historical basis for diagnosis, one must realize the differences between beryllium and other recognized occupational metal intoxicants. The principal difference is the effective dose. In the case of lead or mercury poisoning, for example, the concentrations of metal required for producing intoxication are measured in fractions of a milligram per cubic meter, and exposure over long periods of time is usually experienced before signs of toxicity result. Beryllium, according to present views, can ultimately prove harmful to susceptible individuals at concentrations measured in micrograms per cubic meter,¹³ and fatal granulomatosis may ensue

* The authors wish to express their gratitude for the beryllium analyses to Dr. L. T. Steadman, of the University of Rochester, New York; Dr. Herbert K. Abrams and Mr. Lawrence L. Schmelzer, of the State of California Department of Public Health, and to Dr. J. A. Quigley, of the Health and Safety Division of the United States Atomic Energy Commission.

months or years after a single dose absorbed through the respiratory tract.¹⁴ Whether there are specific differences in the mechanism of intoxication remains to be demonstrated. In view of the extremely small amount of beryllium required to produce progressive disease, the possibility of a "modified immunologic reaction" has been proposed. Sterner and Eisenbud¹⁵ have suggested that an antigen results from the combination of beryllium with body protein, which in turn stimulates the formation of a beryllium specific antibody. Reaction between antigen and antibody is hypothesized as a basis for the inflammatory lesion or granuloma.

The peculiar features of lung disease due to beryllium are emphasized because its wide use requires that physicians consider it among the possible etiologies of obscure pulmonary disorders, even when the occupational aspects are not obvious. Elicitation of a detailed history of employment, including the names of materials handled and the processes involved in the job, may be the only means of establishing an essential link in the chain of diagnostic evidence. While some knowledge of industrial processes is helpful (and might well be expected of physicians practicing in this period of expanding industrialization), it is remarkable what can be gleaned from the patient by dogged and repetitious intelligent inquiry.

The diagnosis of beryllium granulomatosis was considered to be well founded in the case under discussion at a time when his illness was already complicated by hemoptysis and signs of infection proved to be the result of a superimposed pulmonary tuberculosis. The incidence of this complication is not known, but a review of the clinical reports published to date suggests that it is quite unusual. Medical observations of the patient during 1945, 1946 and 1947 included tuberculin skin tests and sputum studies for tuberculosis, which were repeatedly negative. It is likely, therefore, that a primary infection became superimposed upon the granulomatous process due to beryllium some time during the succeeding years. By April, 1950, as a result of extensive pulmonary disease, the patient was extremely hypoxic, and prior to the institution of treatment with cortisone was considered moribund.

The use of cortisone or ACTH was predicated upon the possibility that the cellular inflammatory reaction characteristic of beryllium disease might respond in a manner similar to that of other granulomatous and collagen forming disorders. Although it was soon learned that ACTH was being used in the treatment of several other patients with this disease in the United States and in Canada, the authors had no knowledge of this at the time. Neither were they aware of a deleterious effect in pulmonary tuberculosis, although the dangers of a lytic agent were appreciated, and continuation of antibiotic therapy was considered essential. In any event, the outcome anticipated without resort to new and somewhat heroic treatment was extremely unfavorable and would not have warranted withholding the hormones even had the later reports on their use in tuberculosis been available.

Although this patient's disease was advanced to a degree which would probably have proved irreversible under any therapeutic régime, the clinical response to ACTH was remarkable. The defervescence was undoubtedly due to the effect of the hormone on the tuberculous process, an effect which persisted as long as adequate amounts of ACTH were given, despite the extension of the pathologic process late in the illness. The other impressive phenomena were the remarkable subjective improvement in strength, respiratory function and sense of

well being. Curiously enough, there was no parallel increase in interest in his prior intellectual pursuits. In this respect there was a progressive deterioration in the course of time. Concurrently with the subjective change there was a definite improvement of physical signs, and the lung radiographs showed some suggestion of clearing. These changes are especially remarkable in view of the reported pathologic observations.

No attempt was made to make extensive metabolic studies in the course of this patient's treatment. The studies of Kennedy et al.,¹⁶ Reynolds,¹⁴ Hardy et al.¹⁷ and others indicate that the alterations of function are similar to those resulting from effective use of ACTH in other disorders. In the course of time the relatively benign side reactions of pigmentation, acne and mild Cushing's phenomena appeared. These were not considered material in respect to the patient's illness. His gradual deterioration was considered attributable to progressive pulmonary tuberculosis and chronic hypoxia from respiratory insufficiency.

The pathologic observations indicate that the pulmonary reactions to beryllium and to the products of the tubercle bacillus may become indistinguishable when the two diseases are superimposed. The presence of identifiable bacteria proves conclusively the existence of tuberculosis and, of equal importance, the demonstration of significant amounts of beryllium in the hilar nodes and the lung parenchyma resolves any remaining doubt as to the relationship between the minimal exposure and the patient's illness and death.

SUMMARY

1. Clinical data are presented from a case of chronic granulomatosis of the lungs due to beryllium complicated by pulmonary tuberculosis.
2. The diagnosis of beryllium poisoning requires an appreciation of the peculiar features of this disease from the standpoint of pathogenesis. A detailed occupational history, properly evaluated in the light of the nature of the disease, is essential.
3. The early clinical course in this case was characteristic of beryllium granulomatosis. However, it was adversely affected by the unusual complication of an intercurrent tuberculous infection.
4. ACTH produced a definite clinical remission, with defervescence and improvement of objective as well as subjective manifestations of pulmonary disease. Until the spread of tuberculosis vitiated its beneficial effects, ACTH resulted in improvement of respiratory function as well as gain of weight and strength. Toxic manifestations were not sufficiently marked to warrant discontinuance of treatment.
5. The pathologic findings demonstrate the essential similarity of tissue response to the two etiologic agents involved, namely, beryllium and the tubercle bacillus. The importance of seemingly insignificant exposure to beryllium oxide dust eight years before death is demonstrated by the grave disease manifestations, the etiology of which was still demonstrable by chemical detection of the toxic agent after necropsy.

BIBLIOGRAPHY

1. Shipman, P. L.: History of the beryllium problem, in *Pneumoconiosis*, 1950, Paul B. Hoeber, Inc., New York, pp. 3-10.

2. Hyslop, F., Palmes, E. D., Alford, W. C., Monaco, A. R., and Fairhall, L. T.: The toxicity of beryllium, National Institute of Health Bull. No. 181, U. S. Pub. Health Service, Washington, D. C., 1943.
3. Sprague, G. F., Labelle, C. W., Pettengill, A. G., and Stokinger, H. E.: Initial studies of the toxicity of inhaled beryllium sulfate dust and beryllium metal fume, in Pneumoconiosis, 1950, Paul B. Hoeber, Inc., New York, pp. 326-352.
4. Van Ordstrand, H. S., Hughes, R., De Nardi, J. M., and Carmody, M. G.: Beryllium poisoning, *J. A. M. A.* **129**: 1084-1090, 1945.
5. Hardy, H. L., and Tabershaw, I. R.: Delayed chemical pneumonitis occurring in workers exposed to beryllium compounds, *J. Indust. Hyg. and Toxicol.* **28**: 197-211, 1946.
6. Gardner, L. U.: Generalized pulmonary granulomatosis occurring among workers believed to be exposed to beryllium or its compounds, *Trans. Eleventh Ann. Meeting of Indust. Hyg. Fdt. of Amer., Inc.*, Bull. No. 8, pp. 89-94, Nov. 7, 1946.
7. Martland, H. S., Brodkin, H. A., and Martland, H. S., Jr.: Occupational beryllium poisoning in New Jersey, *J. M. Soc. New Jersey* **45**: 5-15, 1948.
8. De Nardi, J. M., Van Ordstrand, H. S., and Carmody, M. G.: Chronic pulmonary granulomatosis, *Am. J. Med.* **7**: 345-355, 1949.
9. Dutra, F. R.: The pneumonitis and granulomatosis peculiar to beryllium workers, *Am. J. Path.* **24**: 1137-1165, 1948.
10. Chesner, C.: Chronic pulmonary granulomatosis in residents of a community near a beryllium plant: three autopsied cases, *Ann. Int. Med.* **32**: 1028-1048, 1950.
11. Robertson, J. S., Siri, W. E., and Jones, H. B.: Lung ventilation patterns determined by analysis of nitrogen elimination rates; use of the mass spectrometer as a continuous gas analyser, *J. Clin. Investigation* **29**: 577-590, 1950.
12. Steadman, L. T.: Personal communication.
13. Eisenbud, M., Wanta, R. C., Dustan, C., Steadman, L. T., Harris, W. B., and Wolf, B. S.: Nonoccupational berylliosis, *J. Indust. Hyg. and Toxicol.* **31**: 282-294, 1949.
14. Reynolds, P. W.: Beryllium disease from the ceramic industry, *Arch. Ind. Hyg. Occ. Med.* **3**: 575-578, 1951.
15. Sterner, J. H., and Eisenbud, M.: The epidemiology of beryllium intoxication, *Indust. Health Monthly* **11**: 104-105, 1951.
16. Kennedy, B. J., Pare, J. A. P., Pump, K. K., Beck, J. C., Johnson, L. G., Epstein, N. B., Vanning, E. H., and Browne, J. S. L.: Effect of adrenocorticotrophic hormone (ACTH) on beryllium granulomatosis and silicosis, *Am. J. Med.* **10**: 134-155, 1951.
17. Hardy, H. L., Bartter, F. C., and Jaffin, A. E.: Metabolic study of a case of chronic beryllium poisoning treated with ACTH, *Arch. Ind. Hyg. Occ. Med.* **3**: 579-582, 1951.

CLINICAL ASPECTS OF MYXOMA OF THE LEFT AURICLE *

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PRIMARY neoplasms of the heart are rare but are being reported with increasing frequency. Straus and Merliss¹⁸ reported three cases within a year, but quoted figures indicating a frequency of only 0.0017 per cent in 480,331 necropsies.

The endocardial myxoma is the most common as well as the most debated of the primary neoplasms of the heart. More than usual interest has been accorded it because of the occurrence of clinical features simulating those found in some

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of the more common forms of heart disease, and the possibility of surgical extirpation in the future.

This primary tumor is usually pedunculated, and arises most often in the left auricle in the region of the fossa ovalis. McAllen⁴ stated that some 95 such cases of intraauricular myxoma have been reported in the world literature, of which 77 were in the left auricle. It may range in size from that of a pea to that of a large plum, and is usually smooth and globular or polypoid. The surface is usually semitranslucent and yellowish gray in appearance.

The pathology of these tumors has been of considerable interest, especially as to whether they are true myxomas or organized thrombi. Ewing¹⁰ considered that myxoma of the heart was a genuine tumor in the majority of reported cases. Yater¹⁷ emphasized the fact that myxomas are usually found in the auricles, and at times on the heart valves. He believes they arise from a site in the interauricular septum, where it is known that myomatous rests may occur. Thrombi, on the other hand, are usually found in the ventricles. In the majority of cases reported there is scant evidence of past history of endocarditis which would tend to encourage thrombus formation.

Husten²¹ believed the majority of these tumors were organized thrombi. Hamilton-Paterson and Castleden²⁰ discussed their origin in detail and called them "pseudo-myxoma," and suggested that they were pedunculated thrombi, "as all their histological features may be reproduced in organizing blood clots."

The object of this paper is to present an additional case of myxoma of the left auricle and to discuss some clinical aspects which may be of value as criteria for antemortem diagnosis. This case presented the clinical picture of mitral stenosis with congestive cardiac failure, and although the patient was under observation for five months the true diagnosis of intracardiac tumor was revealed only at necropsy. In reviewing the literature I have found no record of a case accurately diagnosed during life.

CASE REPORT

The patient was a 46 year old white married woman (identical twin) who was hospitalized for the first time on December 27, 1950. She complained of upper abdominal distress, described as a "full and tight feeling," and nausea. For several months prior to this she had observed increasing fatigability and breathlessness, palpitation of the heart and rapid pulse rate upon climbing steps or on any mild exertion. There had been no cough, but she had noticed a wheezing type of respiration at intervals and thought she had asthma. There was no past history of rheumatic fever, chorea or syphilis.

The physical examination revealed a well developed, well nourished, alert and cooperative white woman who showed mild shortness of breath but was comfortable lying flat in bed. The temperature was 98°F., the pulse rate was 110 and the respirations were 24. The skin, face and head were normal, and no lymph nodes were palpable. The thyroid gland was diffusely enlarged; the chest was symmetrical, the breasts were small, and the respiratory movements were equal on both sides. Medium moist râles were heard at the bases of both lungs but there were no abnormal percussion notes. The area of cardiac dullness extended 11.5 cm. to the left of the midsternal line in the fifth intercostal space. The heart sounds were not of good quality, and a soft blowing systolic murmur of short duration was heard over the apex region. The apical rate was 110 and the blood pressure was 118/70 mm. of Hg. The peripheral vessels were normal. The abdomen was symmetrical; the liver edge was sharp and



FIG. 1. Direct view of the myxoma, showing its position relative to the mitral orifice.



FIG. 2. A moderately enlarged lateral view of the myxoma, showing its pedicle.

tender, and extended 3 cm. below the costal margin in the midclavicular line. The spleen was not palpable. There was no edema of the lower extremities.

The complete blood count and urinalysis were normal; serologic tests for syphilis were negative; the cholesterol was 180 mg. per cent; the nonprotein nitrogen was 29.5 mg. per cent, and the total protein was 6.8 mg. per cent, with a normal albumin-globulin ratio. A teleroentgenogram showed generalized chamber enlargement of the heart and increased prominence of the lung markings bilaterally. The electrocardiogram revealed right axis deviation, with widening and notching of the P wave in Lead II and a large diphasic P in CF₁ and CF₂. The basal metabolic rate was plus 6 per cent.

A diagnosis of rheumatic heart disease with congestive failure was made. However, the picture was not clear, for there was a question of what part, if any, the enlargement of the thyroid gland played.

The patient was digitalized, a low sodium diet was prescribed, ammonium chloride was used as a diuretic, and on the seventh hospital day she had improved considerably and was discharged with instructions to continue the above regimen.

On February 10, 1951, she was re-admitted to the hospital on the surgical service, where a subtotal thyroidectomy was performed. The pathologic diagnosis was "nodular thyroid showing hyperplasia and involution, with involution predominating." She was discharged on the seventh postoperative day, and her convalescence was uneventful.

On April 6, 1951, she suddenly became severely dyspneic and cyanotic while lying quietly in bed at home, and was hospitalized at once. At this time the neck veins were distended, there was a prominent precordial pulsation, and, in addition to the systolic murmur previously heard at the apex, a low-pitched, rumbling diastolic murmur was heard. The blood pressure was 120/80 mm. of Hg and the heart rate was 100. Marked pulmonary edema was present, the lower edge of the liver extended to the pelvic brim, and free fluid could be demonstrated in the abdominal cavity. Moderate presacral and pretibial edema was present.

Nasal oxygen was administered, Thiomerin was given as a diuretic, and adequate digitalization was maintained. Improvement followed for several days, until another, similar attack occurred. At this time it was noted that the pulse pressure was abnormally low, with the blood pressure varying from 100/85 to 90/80 mm. of Hg. The patient complained of a dull aching type of pain to the left of the lower portion of the sternum.

A teleroentgenogram showed cardiac enlargement greater than at the time of the first admission, four months previously. The electrocardiogram revealed right axis deviation, broad P waves in Lead II and low T waves in all leads. The blood chemistry and other laboratory data were essentially normal with the exception of albumin (plus 2) in the urine.

Repeated attacks of severe breathlessness occurred during the following four weeks. The face, trunk and extremities remained strikingly cold and cyanotic, with severe dependent subcutaneous edema. It was repeatedly observed that the patient preferred to lie flat in bed or turned on the right side than in a propped-up position.

The clinical findings of progressive and relentless congestive heart failure dominated the picture until the patient died suddenly May 15, 1951.

At necropsy a large spherical tumor mass measuring 6 cm. in diameter projected into the left auricular cavity. It was adherent to the interauricular septum in the region of the fossa ovalis by a short pedicle measuring 1 cm. in diameter and 0.5 cm. in length. The external surface was smooth, glistening, semitranslucent and generally yellowish brown in color, with scattered dark red areas of hemorrhage.

Microscopically, the growth consisted of "very loose myxomatous tissue which was uniform throughout; this has an abundant blood supply and is covered externally

by a single thin layer of endothelium. Most of the blood vessels are fairly normal in appearance, but some have clumps of swollen endothelial cells, others have no recognizable endothelial lining. In addition to this, there are numerous clumps and strands of endothelial cells widely scattered throughout the tissue. Some of these strands have a rudimentary lumen, but most of them have no lumen at all." *

CLINICAL FEATURES

Clinical data of myxoma of the left auricle recorded in the literature are rather scanty, and since the presence of such a tumor has not been recognized during life there is no definite characteristic clinical picture. Many of the reported cases are uniform in that the tumors almost filled the atrium and encroached on the mitral orifice, and all terminated fatally.

Of 30 cases reviewed by von Reis,¹ 27 were in women and the majority were between the ages of 30 and 50 years. McAllen⁴ examined 77 recorded cases of myxoma of the left auricle and found that the most common age at death is between 40 and 60 years. He found that females are affected almost three times as often as males.

The clinical picture is usually one of persistent and progressive cardiac failure despite active therapy. This finding has been reported as one of the diagnostic criteria of intracardiac tumors by Yater¹⁷ and Fawcett and Ward.¹⁹ Cardiac murmurs suddenly appearing in a patient who has previously had no murmurs,⁶ or variable auscultatory findings, probably due to changes in relationship of the polypous tumor and the mitral ring, have been reported. The classic murmur of mitral stenosis may be present or absent, but the absence of a history suggesting rheumatic fever is generally regarded as important in the differential diagnosis. However, a positive history of rheumatic fever is recorded occasionally. Dexter and Work¹² described a case associated with rheumatic heart disease, and Anderson and Dmytryk¹⁶ reported a case having stenosis of the aortic valve with thickened adherent calcified leaflets.

The duration of the illness from onset of symptoms to death is short in the majority of cases of myxoma of the left auricle. The course is dependent upon the size of the tumor, the rapidity of its growth and the length of the pedicle. The prominent findings of severe breathlessness, cyanosis, edema, low pulse pressure and sudden attacks of fainting^{6, 11} are explained by the encroachment of the tumor upon the mitral orifice. Attacks of syncope or unconsciousness^{1, 8} have been described. These attacks are probably due to sudden temporary blocking of the auriculoventricular orifice by the tumor. The length of the pedicle and the size and mobility of the tumor may explain the variations in the cardiac signs reported by different authors.

Thompson¹³ and Gilchrist and Millar¹⁴ reported cases that died suddenly. Other writers have described a similar mode of death; Yater¹⁷ states that sudden death may occur in patients without previous cardiac history. It would seem that the mechanism in such cases is complete blocking of the mitral orifice by the tumor, giving rise to the picture of acute left ventricular failure. In one of McAllen's cases⁴ the tumor extended through the mitral orifice, expanded into the upper part of the ventricle, and showed a deep groove at the level of the mitral ring.

* Examination made by V. H. Moon, M.D.

The postural factor has been a prominent feature in the production of symptoms,^{3, 4, 6} yet in such cases there is no uniformity concerning the position most likely to give relief or to produce symptoms. Variable auscultatory findings with change of the bodily position of the patient have been described. This is probably due to changes in the relationship of the tumor and the mitral ring. A number of cases have been described where, in the presence of severe cyanosis and dyspnea, the patient preferred to lie flat in bed.

Electrocardiograms have been recorded in a few of the reported cases of primary cardiac tumors.^{4, 11, 13, 14} Benign tumors do not usually interfere with the conducting mechanism of the heart,² while the arrhythmias which have been observed have usually occurred in the presence of malignant tumors. In cases of myxoma in which there is gradual obliteration of the auricle by the ever-growing tumor, variable degrees of cardiac failure may develop; certain electrocardiographic changes may be expected in such instances. These changes may reflect damage in the left auricle and in the right ventricle and auricle. In Burnett and Davidson's¹⁵ case there was right axis deviation with normal P waves, low voltage T₁ and T₂ and slight depression of S T₃. P wave changes have been described as resembling those seen in mitral stenosis.

The value of the electrocardiogram as an aid to differential diagnosis of auricular myxoma has not yet been established.

Occasionally embolic phenomena produce variable neurologic symptoms^{5, 9} which complicate the picture of heart failure. It is presumed these result from emboli becoming detached from the tumor itself⁴ or from thrombi forming on its surface.

Several cases^{2, 7, 9, 14} presenting abnormal radiologic outlines have been described. In Coulter's case⁹ the "teleroentgenogram showed moderate enlargement of the cardiac silhouette, with prominence of the pulmonary artery," while in the case reported by Bennett et al.⁷ a large bulge in the region of the pulmonary conus was noted. In this case the radiologic outline revealed only generalized chamber enlargement of the heart. It would seem that the x-ray has been of little value as an antemortem diagnostic aid in the cases reported.

COMMENT

Myxoma of the left auricle is extremely rare and the diagnosis exceedingly difficult. Neither the x-ray nor the electrocardiograph has furnished dependable clues to its recognition. The possible presence of auricular myxoma might be suggested by persistent progressive cardiac deficiency, not myocardial in origin and not due to any apparent cardiac lesion, and entirely unresponsive to treatment. Its symptoms and signs seem to result from mechanical interference with left cardiac function, chiefly at the mitral orifice. Whether these may suffice to establish the diagnosis prior to death is problematic.

SUMMARY

A case of myxoma of the left auricle occurring in a 46 year old woman is described.

Some of the more common clinical features have been discussed as an aid to antemortem diagnosis.

BIBLIOGRAPHY

1. von Reis, G.: Clinical aspects of endocardial myxoma situated in the left atrium, *Acta med. Scandinav.* **133**: 214-219, 1949.
2. Macoun, S. J. R.: Cardiac myxoma, *Thorax* **4**: 39-43, 1949.
3. Allison, D. R., and Susman, W.: Myxoma of the heart, *Lancet* **2**: 11-12, 1949.
4. McAllen, P. M.: Myxoma of left auricle, *Brit. M. J.* **1**: 932-934, 1950.
5. Mills, P., and Philpott, M.: Myxoma of heart with neurological signs, *Brit. Heart J.* **13**: 115-117, 1951.
6. Weinstein, M. S., and Arata, J. E.: Mitral stenosis and insufficiency produced by cardiac "myxoma," *Am. Heart J.* **38**: 781-787, 1949.
7. Bennett, D. W., Konigsberg, J., and Dublin, W.: Primary tumor of the heart producing an unusual cardiac shadow in the roentgenogram, *Am. Heart J.* **16**: 117-122, 1938.
8. Friedberg, C. K.: Diseases of the heart, 1949, W. B. Saunders Company, Philadelphia, p. 995.
9. Coulter, W. W.: Myxoma of the heart (left auricle), *Arch. Path.* **49**: 612-617, 1950.
10. Ewing, J.: Neoplastic diseases, 1928, W. B. Saunders Company, Philadelphia, p. 188.
11. Houck, G. H., and Bennett, G. A.: Polypoid fibroma of the left auricle (so-called cardiac myxoma) causing a ball-valve action, *Am. Heart J.* **5**: 787-794, 1930.
12. Dexter, R., and Work, J. L.: Myxoma of the heart, *Arch. Path.* **32**: 995-999, 1941.
13. Thompson, R. B.: A case of myxoma of the left auricle, *Brit. Heart J.* **6**: 23-26, 1944.
14. Gilchrist, A. R., and Millar, W. G.: Paroxysmal auricular tachycardia associated with primary cardiac tumor, with pathological report, *Edinburgh M. J.* **43**: 243-258, 1936.
15. Burnett, W., and Davidson, J. I.: A case of myxoma of the heart, *Brit. Heart J.* **7**: 180-182, 1945.
16. Anderson, W. A. D., and Dmytryk, E. T.: Primary tumor of heart containing epithelium-like elements, *Am. J. Path.* **22**: 337-349, 1946.
17. Yater, W. M.: Tumors of the heart and pericardium, *Arch. Int. Med.* **48**: 627-666, 1931.
18. Straus, R., and Merliss, R.: Primary tumor of the heart, *Arch. Path.* **39**: 74-78, 1945.
19. Fawcett, R. E. M., and Ward, E. M.: Cardiac myxoma; clinical and pathological study, *Brit. Heart J.* **1**: 249-260, 1939.
20. Hamilton-Paterson, J. L., and Castleden, L. I. M.: Intracardiac tumors, *Brit. Heart J.* **4**: 103-114, 1942.
21. Husten, K.: Ueber Tumoren und Pseudo-tumoren des Endocards, *Beitr. z. path. Anat. u. z. allg. Path.* **71**: 132, 1922 (cited by Macoun).

UNUSUAL TOXICITY TO TRIETHYLENE MELAMINE IN A CASE OF CHRONIC MYELOGENOUS LEUKEMIA*

By ALVIN SLIPYAN, M.D., *Elmhurst, N. Y.*

THE search for a chemotherapeutic agent in leukemia is still in progress. This drug should have a wide margin of safety, and be very effective and easy to administer. The most recent of the drugs tried clinically is triethylene melamine.

As far back as 1946, when the nitrogen mustards were introduced into medical practice for the palliative treatment of the lymphomas, leukemias, etc. by Rhodes¹ and a host of other investigators reporting in various journals, work had already

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The drug was supplied by Dr. J. M. Ruegsegger, of the Lederle Laboratories Division, American Cyanamid Company.

begun to improve this form of therapy. Changing the structural formula of the mustards for new drugs was a logical sequence. Lewis and Crossley² discovered that triethylene melamine, a chemical with nitrogen mustard-like activity, was effective orally in inhibiting tumor growth in animals.

In figure 1, note the comparison of the structural formulas of methyl-bis (2-chloroethyl) amine and triethylene melamine. The ethylenimino groups of triethylene melamine are similar to the ethylenimonium transformation product of methyl-bis (2-chloroethyl) amine.³

The chemotherapeutic activity is attributed to the ethylenimino ring, which is similar to the active hydrolysate of nitrogen mustard when this material is dissolved in water.⁴ It was found that triethylene melamine, although acting simi-

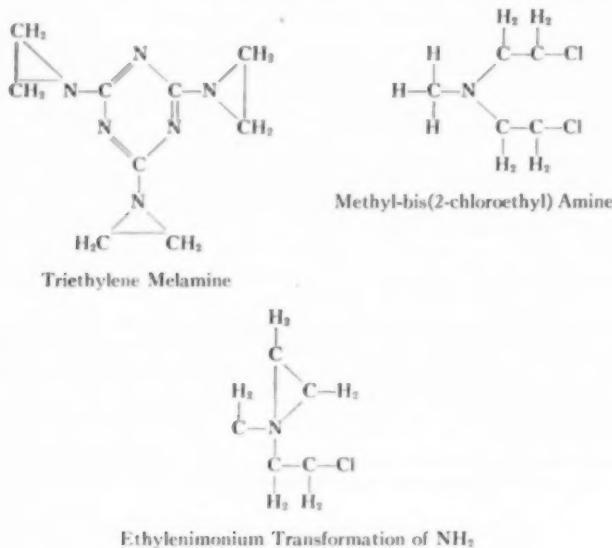


FIG. 1.

larly, caused inconstant and less severe nausea and vomiting.⁵ The work of Burchenal et al.⁶ has shown that this drug is effective in prolonging the survival time of leukemic mice.

The first clinical report was presented at a meeting of the Association of American Physicians in May, 1950, by C. P. Rhodes et al.,⁸ and dealt with results of this drug in 46 cases of Hodgkin's disease, leukemia and related diseases. Philips and Thiersch⁷ have reported the comparative toxic effects of nitrogen mustard and triethylene melamine and have found that triethylene melamine produced atrophy of all hematopoietic tissue and injury to the intestinal epithelium. The same toxic effect was also reported by Silverberg and Dameshek.⁸ Graef et al.⁹ found that the delayed lethal effects of triethylene melamine closely resembled those of nitrogen mustard in mice and rats, in that death occurred in three to seven days after a M.I.D. Burchenal et al.¹⁰ showed that when two to four times

the acute LD 50 of triethylene melamine was injected into a leukemic mouse, the leukemic cells were inactivated within two hours, and that inactivation was measured by the failure of the leukemic cells to survive transplantation into a susceptible strain.

The following case report is one of unusual bone marrow depression by a comparatively small dose of triethylene melamine, and should accentuate the dangers inherent in this form of therapy.

CASE REPORT

A 66 year old woman, mother of four children and widowed for 10 years, had complained of easy fatigability for many years. There were no other complaints as far as she could remember. In 1945 she was found to have an enlarged spleen, and a blood count revealed the typical picture of chronic myelogenous leukemia. The white blood count was 200,000, with 3 per cent myeloblasts, 55 per cent myelocytes, 5 per cent eosinophils, 5 per cent immature polys, 7 per cent monocytes and 21 per cent lymphocytes. The bone marrow confirmed the diagnosis. The patient was treated symptomatically and felt well for two years. In 1947 a complete relapse ensued; the major symptoms were fever, weakness, anorexia, night sweats, weight loss and generalized bony aches. The spleen at this time had enlarged and filled the entire left abdomen. The bone marrow and white blood count were still typical of chronic myelogenous leukemia. Urethane was given in full dosage but was discontinued after one week's treatment because it caused severe nausea and vomiting. This therapy apparently induced a remission, so that after three weeks the patient felt almost entirely well. The blood count was normal except for a 15 per cent myelocyte report. The spleen regressed and was palpable just below the rib margin. After eight months another relapse occurred and the same clinical findings and blood studies were encountered. Another course of urethane was started but had to be discontinued after six days because of the patient's severe nausea and vomiting. Another remission took place which lasted two months. The relapse now did not respond to urethane, which was tried in capsule, enteric coated pills and even in especially flavored solution. A course of 6.3 mg. nitrogen mustard on four successive days was given. Moderate nausea and vomiting were produced but another remission was obtained. The blood reports were normal except for the platelet count, which dropped from 200,000 to 75,000 for one month and then rose to normal. This remission was so complete that the patient returned to work for the first time in years, and, on being examined by another physician, who apparently did some blood studies, she was told that she had never had leukemia.

In October, 1951, she suffered another relapse and left her physician and returned for more treatment. Urethane was completely unsuccessful now; and the nitrogen mustard induced only a partial remission, so that she never felt entirely well. The bone marrow and blood still reflected the disease state. After several months another relapse brought her back. This time the patient was given cortisone, 300 mg. daily for three weeks. A definite euphoria was obtained but the blood and marrow picture did not change. During the cortisone therapy she developed a right lower lobar pneumonia which responded to large daily doses of penicillin.

In April, 1952, the patient was quite ill. Marked loss of weight, fever, night sweats and cachexia were prominent. The blood count revealed red blood cells of 3.4 million, with 10 gm. hemoglobin. While blood cell count was 280,000, with 83 per cent myelocytes and 192,000 platelets. The bone marrow report showed the same leukemic state. Triethylene melamine was started, and the method of D. A. Karnofsky was tried. This consisted of giving the drug in the morning on a fasting stomach with a little water, and no food for several hours after that. The patient was given

5 mg. of the drug on two successive days. It produced only slight nausea and no intolerable effect of the drug was noticed. The patient began to improve after four days, and a complete remission was present after two weeks. The blood picture, although improved, still showed white blood cells of 137,000 and 112,000 platelets, with 48 per cent myelocytes. Clinically the patient was better. The spleen, which had previously almost filled the entire abdomen (the largest I have ever seen), was barely palpable. On May 20, 1952, a sudden petechial outburst occurred over the body and mucous membranes. A severe occipital headache was present and a hemorrhage into the right conjunctiva was present. A blood count now revealed red blood cells of 930,000; hemoglobin 5.6 gm.; white blood cells, 2,550; myelocytes, 16 per cent; platelets, 10,000. In spite of almost continuous blood transfusion the patient began to have severe gastrointestinal bleeding, with a decrease in the entire blood count. The white blood cells dropped to 950 and the platelets to 5,000. After a severe hemorrhage from the gastrointestinal tract, the patient died on June 1, 1952.

COMMENT

This case demonstrates the severe bone marrow depression that can occur with triethylene melamine. The unusual severity of the hematopoietic depression from so small a dose of the drug indicates the great caution that must be exercised. As more experience with the drug is accumulated similar reactions will surely be reported. Karnofsky et al.¹¹ reported on eight cases with chronic myelogenous leukemia treated with triethylene melamine orally and no case of fatal bone marrow depression occurred with so small a dose. Wright et al.¹² reporting on 28 adults with neoplastic disease, of which one case was a chronic myelogenous leukemia, said that the only toxicity was that of nausea and one episode of weakness on the second to fifth days of the first, fourth, fifth and sixth courses. This case of chronic myelogenous leukemia received a total of 90 mg. in 265 days, with excellent results. The first course consisted of 10 mg. for two days. Silverberg and Dameshek⁸ reported on eight cases of chronic myelogenous leukemia treated orally with triethylene melamine. No fatality occurred and no instance of such marked sensitivity in the bone marrow was noted, and no case of less than 50,000 platelets was seen in all 46 patients whose treatment with the drug has been reported. Hansen and Bichel¹³ described a case of chronic myelogenous leukemia treated with triethylene melamine which at first showed much improvement and finally ended with a fatal aplastic anemia. However, the dose of the drug was much higher than that used in this case. Antonio Rottino,¹⁴ reporting from the Hodgkin's Disease Laboratory of the St. Vincent's Hospital in New York, stated that the average dose of triethylene melamine producing aplastic anemia was in the neighborhood of 45 mg. or more, administered in a period of three weeks.

The dosage schedule of triethylene melamine is still in the experimental stage, and revision will come with more experience. The severe sensitivity of the bone marrow exhibited in this case can only serve as a warning that this is a possibility.

SUMMARY

A brief review of a new drug, triethylene melamine, in the treatment of chronic myelogenous leukemia is presented, and a case report showing a severe fatal bone marrow depression after a very small dose.

BIBLIOGRAPHY

1. Rhodes, C. P.: Nitrogen mustard in the treatment of neoplastic disease, *J. A. M. A.* **131**: 656 (June 22) 1946.
2. Lewis, M. R., and Crossley, M. L.: Retardation of tumor growth in mice by oral administration of ethylenimine derivatives, *Arch. Biochem.* **26**: 319 (April) 1950.
3. Philips, F. S.: Recent contributions to the pharmacology of bis (2-haloethyl) amines and sulfides, *Pharmacol. Rev.* **2**: 281, 1950.
4. Burchenal, J. H., Johnston, S. F., Cremer, M. A., Webber, L. F., and Stock, C. C.: Chemotherapy of leukemia. Effect of 2, 4, 6, triethylenimino s-triazine and related compounds on transplanted mouse leukemia, *Proc. Soc. Exper. Biol. and Med.* **74**: 708 (Aug.) 1950.
5. Rhodes, C. P., Karnofsky, D. A., Burchenal, J. H., and Craver, L. F.: Triethylene melamine in the treatment of Hodgkin's disease and allied neoplasms, *Tr. A. Am. Physicians* **63**: 136, 1950.
6. Burchenal, J. H., Crossley, M. L., Stock, C. C., and Rhodes, C. P.: The action of certain ethylenimine (azericidine) derivatives on mouse leukemia, *Arch. Biochem.* **26**: 321 (April) 1950.
7. Philips, F. S., and Thiersch, J. H.: The nitrogen mustard-like actions of 2, 4, 6, tris (ethylenamino) s-triazine and other bis (ethylenimines), *J. Pharmacol. and Exper. Therap.* **100**: 398 (Dec.) 1950.
8. Silverberg, J. H., and Dameshek, W. D.: Use of triethylene melamine in treatment of leukemia and leukosarcoma, *J. A. M. A.* **148**: 1015 (Mar.) 1952.
9. Graef, I., Karnofsky, D. A., Jaeger, V. B., Krichesky, B., and Smith, H. W.: The clinical and pathological effects of the nitrogen mustards in laboratory animals, *Am. J. Path.* **24**: 1, 1948.
10. Burchenal, J. H., Johnston, S. F., Stock, C. C., Crossley, M. L., and Rhodes, C. P.: Chemotherapy of leukemia: the effect of 2, 4, 6, triethylenimino-s-triazine, and related compounds in transplanted mouse leukemia, *Proc. Soc. Exper. Biol. and Med.* **74**: 708-712 (Aug.) 1950, abstracted in *Cancer Research* **10**: 208, 1950.
11. Karnofsky, D. A., Burchenal, J. H., Armistead, G. C., Jr., Southam, C. M., Bernstein, J. L., Graver, L. F., and Rhodes, C. P.: Triethylene melamine in the treatment of neoplastic disease, *Arch. Int. Med.* **87**: 477 (April) 1951.
12. Wright, J. C., Prigot, A. A., Wright, L. T., and Arons, I.: Further observations on the use of triethylene melamine in neoplastic diseases, *Arch. Int. Med.* **89**: 387, 1952.
13. Hansen, P. B., and Bichel, J.: Triethylene melamine treatment of Hodgkin's disease and other malignant diseases, *Nord. Med.* **47**: 43-74 (Jan. 11) 1952.
14. Rottino, A.: Triethylene melamine in the treatment of Hodgkin's disease and other lymphomas, *New York State J. Med.* **52**: 346 (Feb. 1) 1952.

THE RELIEF OF TIC DOULOUREUX WITH STILBAMIDINE *

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A REVIEW of the properties of stilbamidine (4:4' stilbenedicarboxamidine) and observation of patients treated for various diseases with the drug revealed that

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its late chronic toxicity was confined to an unusual neuropathy. The progressive sensory changes of paresthesia, hypalgesia and anesthesia, usually confined to the face, were noted two to five months after a course of stilbamidine.^{1, 4, 5, 12, 13, 15, 16} Napier and Sen Gupta¹³ found a subjective disturbance of sensation over various distributions of the fifth cranial nerves. They suggested that the lesion was in the sensory nucleus of the trigeminal nerve in the pons. Collard and Nevin⁵ also considered the lesion to be in the nucleus of the fifth nerve and, in addition, in the descending nucleus.

The mechanism of the neuropathy is totally obscure. Ostler and Fidler¹⁴ administered fresh solutions of stilbamidine to 10 dogs and found evidence of macroscopic and microscopic damage to the brain. In five dogs in which clinical evidence of damage was not observed, microscopic examination still showed alterations in the brain.

With this background, the concept of deliberately using stilbamidine to evoke the specific neuropathy as a treatment for tic douloureux was suggested by Dr. Frank R. Ford, of Baltimore, Maryland. The substitution of a hypesthesia for the sharp pain of tic douloureux by using stilbamidine might be a significant advance in the treatment of this painful disease. Even if not so completely effective for the relief of pain as section of the portion or portions of the involved fifth cranial nerve, stilbamidine might offer palliation in elderly patients in whom operation was contraindicated.

When properly prepared and administered, stilbamidine is not toxic except for the late neuropathy. The drug should be dissolved in a solution of 5 per cent glucose in distilled water and should be put into solution just before being given intravenously.

Solutions of stilbamidine are markedly affected by even short exposure to light.^{2, 6, 8, 10} Fulton⁶ found a sixfold increase in toxicity after exposure of the solution to light for two days. Changes were also demonstrated after an exposure of one-half hour to winter sunlight, with a significant loss in therapeutic properties. This observation was confirmed by Barber, Slack and Wien,² who reported a four- to fivefold increase in toxicity of 0.5 per cent solutions of stilbamidine exposed to sunlight.

Fulton and Goodwin⁷ have demonstrated that the addition of stilbamidine to human serum in concentrations greater than 0.5 per cent results in precipitation as a base. For therapeutic use, 0.15 gm. of stilbamidine is dissolved in 100 c.c. of 5 per cent glucose in distilled water. Transient toxic reaction may be avoided by slowly giving the freshly prepared solution intravenously.⁹ Such symptoms may include a fall in blood pressure, generalized formication, sweating, breathlessness, dizziness, nausea, epigastric discomfort, vomiting, salivation, incontinence of feces and urine, and a puffy sensation of the face and eyelids.

Deaths due to delayed poisoning have been reported by Bowesman³ and Kirk and Henry.¹¹ The fatalities were due to combined hepatic and renal injury. It should be noted that solutions were used which had been prepared in England and shipped to Africa by air. It is now known that such solutions were unstable and became toxic. These reports emphasize the fact that solutions of stilbamidine must be prepared just before administration.

CASE REPORT

An 80 year old Negro woman, first seen on March 20, 1952, had typical attacks of tic douloureux on the right side for about six months. The individual attacks were severe, and prevented eating and interrupted sleep. The paroxysms occurred two to three times daily, and often would come in showers of pain lasting as long as 20 minutes. The pain extended classically into the malar and mandibular areas.

A severe degree of arteriosclerotic heart disease with a blood pressure of 210/110 mm. of Hg was present. The neurologic examination was normal.

The diagnosis of tic douloureux was plain. The advanced age of the patient and the presence of severe arteriosclerotic heart disease were contraindications to operation. She therefore seemed a good candidate for treatment with stilbamidine.

Stilbamidine,* 0.15 gm., in 100 c.c. of 5 per cent glucose in distilled water, was given intravenously daily from April 9 through April 23. On April 22 the patient reported that the attacks were less frequent and severe. On July 18 the patient had no complaint of pain about the right side of the face. She was able to eat without pain, and her sleep was not interrupted by pain. A hypesthesia of both sides of the face was present but this caused no difficulty.

SUMMARY

Stilbamidine, by virtue of producing a unique, late appearing neuropathy of the fifth cranial nerves, may be valuable in the treatment of tic douloureux. The result obtained in the patient reported is encouraging, and further trial of the treatment of tic douloureux with stilbamidine is being made.

BIBLIOGRAPHY

1. Arai, H., and Snapper, I.: The influence of stilbamidine upon kidney function, liver function and peripheral blood in multiple myeloma. Neurologic sequelae of stilbamidine therapy, *New York State J. Med.* **47**: 1867-1874 (Sept.) 1947.
2. Barber, H. J., Slack, R., and Wien, R.: Increase in toxicity of stilbamidine solution on exposure to light, *Nature, London* **151**: 107-108 (Jan. 23) 1943.
3. Bowesman, C.: A short report on the use of 4:4' diamidene stilbene in the treatment of human sleeping sickness, *Ann. Trop. Med.* **34**: 217-222 (Dec.) 1940.
4. Collard, P. J., and Hargreaves, W. H.: Neuropathy after stilbamidine treatment of kala-azar, *Lancet* **2**: 686-688 (Nov. 8) 1947.
5. Collard, P., and Nevin, S.: Affection of the trigeminal nerve nucleus and central gray matter of the spinal cord following the administration of stilbamidine, *Proc. Roy. Soc. Med.* **40**: 87-88 (Nov. 7) 1946.
6. Fulton, J. D.: Studies in chemotherapy. XXIII. Toxicity and therapeutic action of certain aromatic diamidines after exposure to light, *Ann. Trop. Med.* **37**: 48-59 (April) 1943.
7. Fulton, J. D., and Goodwin, T. W.: Studies in the estimation, absorption and precipitation of stilbamidine, *J. Pharmacol. and Exper. Therap.* **84**: 34-45 (May) 1945.
8. Fulton, J. D., and Yorke, W.: Studies in chemotherapy. XXXI. The increased toxicity of old solutions of stilbamidine, *Ann. Trop. Med.* **36**: 134-136 (Sept.) 1942.
9. Haedicke, T. A., and Greenspan, E. M.: Massive stilbamidine therapy of multiple myeloma. Report of a case, *Am. J. Clin. Path.* **19**: 634-638 (July) 1949.
10. Henry, A. J.: Instability of stilbamidine in aqueous solution, *Nature, London* **152**: 690-692 (Dec. 11) 1943.
11. Kirk, R., and Henry, A. J.: Observations on the toxicity of stilbamidine, *Ann. Trop. Med.* **38**: 99-118 (Sept.) 1944.

* The stilbamidine isethionate was supplied by The W. S. Merrell Company.

12. Miller, J. M., Long, P. H., and Schoenbach, E. B.: Successful treatment of actinomycosis with stilbamidine, *J. A. M. A.* **150**: 35 (Sept. 6) 1952.
13. Napier, L. E., and Sen Gupta, P. C.: A peculiar neurological sequel to administration of 4:4' diamidino-diphenyl ethylene (M and B 744), *Indian M. Gaz.* **77**: 71-74 (Feb.) 1942.
14. Ostler, E. G., and Fidler, H. K.: Cerebral lesions produced in healthy dogs by the intravenous injection of 4:4' diamidino-stilbene, *Tr. Roy. Soc. Trop. Med. and Hyg.* **39**: 533-538 (June) 1946.
15. Schoenbach, E. B., Miller, J. M., and Long, P. H.: The treatment of systemic blastomycosis with stilbamidine, *Ann. Int. Med.* **37**: 31-47 (July) 1952.
16. Sen Gupta, P. C.: Observations on the neuropathic sequel of diamidino-stilbene in kala-azar, *Indian M. Gaz.* **78**: 537-543 (Nov.) 1943.

DIABETES MELLITUS, HYPERTHYROIDISM AND ADDISON'S DISEASE IN ONE PATIENT *

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A REVIEW of the literature reveals no well documented case of the existence of diabetes mellitus, hyperthyroidism and Addison's disease in one patient. Rountree and Snell¹ reported one such case, but some doubt was cast on its validity by Rhind and Wilson.²

CASE REPORT

The patient, a Russian-born white woman who was 48 years old at the time of her initial hospital admission, entered the Bronx Hospital for the first time on September 29, 1947, in a stupor, with a history of nausea and vomiting of two days' duration. Past history revealed that the patient had had typhoid fever in 1914 and influenza in 1919. Family history was negative except that one child of the patient had died of leukemia at seven and one half years of age. The patient had been in excellent health, sufficiently energetic to be able to do housekeeping and office work at the same time until the early part of 1947, when she began to notice a feeling of exhaustion and extreme thirst and hunger, and passed large quantities of urine. As a result of blood and urine findings a diagnosis of diabetes mellitus was made. The diabetes was controlled by diet alone, and the patient's weight was maintained at 132 pounds.

Thirty-six hours prior to the time of the first hospital admission the patient developed acute gastroenteritis following a dietary indiscretion. On the day of admission she became semi-stuporous. Physical examination on admission revealed an acutely ill patient who was somewhat somnolent but responded to questioning. Exophthalmos was present. The eyeballs were firm. The tongue was dry. The thyroid gland was enlarged. The heart was not enlarged but the apex beat was diffuse and forceful, and the heart rate was 160 per minute with runs of extrasystoles or paroxysmal fibrillation. Blood pressure was 160/70 mm. of Hg. The lungs, abdomen and extremities were normal. The blood sugar was 470 mg. per 100 c.c. and the CO₂ combining power was 20 vol. per cent. The urine contained 1.4 per cent glucose and 2 plus acetone. The electrocardiogram on the day after admission showed auricular flutter with 2:1 block; eight days later it showed regular sinus rhythm and

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evidence of myocardial damage. The basal metabolic rate one week after admission was plus 77. The patient was treated with intravenous glucose and regular insulin and potassium iodide until the diabetes was brought under control. She was then placed on a regimen of 15 units of a 2:1 mixture of regular and protamine zinc insulin, 50 mg. of propylthiouracil four times daily, and saturated solution of potassium iodide, five drops three times daily. She was discharged improved on the above therapy.

For the next four years the patient continued to take 15 units of PZI daily and propylthiouracil. During this time she maintained her weight and was asymptomatic. In the fall of 1950 she stopped taking propylthiouracil without medical advice. During the summer of 1951, after several months at the seashore, she developed a skin tan that was not unusual for her. In early September she noted unusual sweating in the morning and afternoon. During the next few months she lost 20 pounds and became progressively weaker and more drowsy. During the month of December she vomited frequently, without relation to meals. She was re-admitted to The Bronx Hospital on December 11, 1951, because of increasing weakness, anorexia and weight loss. Physical examination at that time revealed a thin, chronically sick looking woman. Exophthalmos with lid-lag and defective ocular convergence were present. There was a small area of pigmentation at the angle of the mouth but none on the mucous membranes or tongue. The thyroid gland was enlarged. The heart rate was 112 per minute, with sinus rhythm. Blood pressure was 110/60 mm. of Hg. The skin was diffusely tanned in the areas usually left uncovered by a bathing suit. A fine tremor of the fingers was present. The palms were moist but the skin was not abnormally warm. Laboratory studies showed the following: red blood cell count, 4.7 million per cubic millimeter; white blood cells, 4,000 per cubic millimeter, with 47 per cent polymorphonuclears, 46 per cent lymphocytes, 7 per cent monocytes; hemoglobin, 14.2 gm. The urine had a specific gravity of 1.012, acid reaction, a trace of albumin and no sugar. Blood sugar was 169 mg., blood urea nitrogen 27.3 mg., and blood cholesterol 132 mg. per 100 c.c. Plasma sodium chloride was 545 mg. per 100 c.c.; serum sodium, 141 mEq., and serum potassium, 6.8 mEq. per liter. The basal metabolic rate was plus 9. X-ray of the chest was negative, and the electrocardiogram was within normal limits.

It was noted that, throughout this hospital stay, the patient's diabetes was not at all difficult to control. Her urine remained sugar-free despite the fact that she was given no insulin and was on a diet containing 175 gm. carbohydrate, 100 gm. protein and 90 gm. fat. However, vomiting occurred intermittently despite all therapy. A radioactive iodine uptake study showed a 60 per cent uptake in 24 hours, despite a basal metabolic rate of plus 9. The pulse rate was between 100 and 120 per minute. A therapeutic dose of radioactive iodine (I^{131}) was given on December 13. The patient was discharged on January 5, 1952, and advised to take Lugol's solution, five drops four times daily.

During the next month the patient's weight did not increase; she continued to vomit and developed marked anorexia, and the smell of food was enough to make her gag. Because of these complaints she was re-admitted to The Bronx Hospital on February 14, 1952. At that time it was found that her blood pressure was 80/60 to 88/80 mm. of Hg. The diffuse tanning of the skin described before was still present but, in addition, there were spots of dark bluish-gray pigment on the tongue and buccal mucosa. Brownish freckle-like deposits were noted on the face. There were scattered pigmented areas on the palms and soles, on the elbows, and in traumatized scar-tissue sites over the tibial areas of the legs. The patient appeared critically ill. No thyroid tissue was palpable. The heart rhythm was regular but the rate still was between 100 and 110 per minute. No abdominal organs were palpable.

Laboratory examinations: Blood count showed 5.1 million red cells per cubic milli-

meter; 6,500 white cells, with 60 per cent polymorphonuclears, 30 per cent lymphocytes, 8 per cent monocytes and 2 per cent eosinophils; hemoglobin was 14.3 gm. Urinalysis showed 3 plus sugar and 3 plus acetone. Injection of 20 units of regular insulin at this time caused a hypoglycemic reaction. Fasting blood sugar the day after admission was 92 mg. per 100 c.c. Blood urea nitrogen was 37.4 mg. per 100 c.c. This was believed due to prerenal azotemia. Later urine examinations showed concentration to a specific gravity of 1.018; there were no albumin or formed elements. On February 21 the serum sodium was found to be 108 mEq. per liter, and serum potassium 7.5 mEq. A glucose tolerance test, using oral ingestion method, showed a fasting blood sugar of 159; after one-half hour, 220; after one hour, 332; after two hours, 347; after three hours, 392. Blood cholesterol was 154 mg. per 100 c.c., with 52 per cent esters. A gastric aspiration showed no free acid in any specimen, even after injection of histamine; maximal total acidity in any specimen was 53 units. Because of the patient's profound weakness during the early part of her stay the basal metabolic rate could not be determined until March 10, at which time it was plus 1. Total blood proteins were 6.1 gm., with albumin 3.3 gm. and globulin 2.8 gm. per 100 c.c. The electrocardiogram on admission showed low voltage and low T-waves in all limb leads (despite high serum potassium) and a prolonged Q-T duration, 0.36 second; the ST transition was depressed in Leads II and III, and a sinus tachycardia, rate 110, was noted. X-ray examination of the skull, sella turcica and abdomen was negative. Gastrointestinal x-ray series was negative. A skin biopsy was done and the tissue tested for pigment; melanin was found, but no hemosiderin. Tuberculin test, with purified protein derivative in 1:10,000 dilution, was read as positive, grade 2. Skin test for iron, using potassium ferrocyanide, was negative. A Kepler water test, part 1, showed a night specimen volume of 400 c.c. and a total all-day volume of only 125 c.c. Part 2 was not done. Excretion of 17-ketosteroids was 3.4 mg. in 24 hours. The Thorn test was done three times and showed the following eosinophil counts:

First test, before ACTH: 330/cu. mm. Four hours after ACTH: 405/cu. mm.

Second test, before ACTH: 370/cu. mm. Four hours after ACTH: 430/cu. mm.

Third test, before ACTH: 320/cu. mm. Four hours after ACTH: 295/cu. mm.

Immediately after the serum sodium and potassium levels were determined the patient was started on therapy with desoxycorticosterone acetate (DCA) and sodium chloride. DCA, 25 mg., was injected daily for eight days; this dose was gradually reduced to 5 mg. daily. Six grams of sodium chloride per day, in divided doses, were given by mouth. Within two days after therapy was started the patient stopped vomiting and began to feel stronger. Five days later her blood pressure had risen to 110/60 mm. of Hg. The serum sodium rose to 139 mEq. per liter and the potassium fell to 5.1 mEq. Edema of the dorsum of the feet appeared and the DCA was discontinued and an attempt was made to maintain the patient only on 6 gm. of sodium chloride daily. She did well on this regimen for five days but then began to complain of weakness and anorexia. She was then given Percorten Linguelets (Ciba Pharmaceutical Co.), 4 mg. sublingually daily. This medication was continued for one week, but the patient continued to be anorexic and weak, and lost four pounds in weight. During this time her serum sodium fell to 123 mEq. and potassium rose to 6.4 mEq. Treatment with DCA was therefore resumed, and 5 mg. intramuscular injections were given daily. The patient began to improve immediately.

The patient is now maintained in good condition with 1 mg. DCA and 2 gm. sodium chloride daily. Her blood pressure has stabilized at 140/90 mm. of Hg, and she is gaining weight; her last serum sodium level was 140 mEq. per liter, and serum potassium was 5.4 mEq. During the early period of this hospital stay her diabetes was controlled without insulin, but during the latter part, with her increase in appetite, it was found necessary to give her NPH insulin, 35 units daily, with a 2,100 calorie diet.

COMMENT

In this patient a definite diagnosis of diabetes mellitus and hyperthyroidism was established in 1947, and the presence of Addison's disease was demonstrated in February, 1952. A question may be raised concerning the patient's signs and symptoms during her hospitalization in December, 1951. Because of the tachycardia, weight loss, past history of hyperthyroidism and a radioactive iodine uptake of 60 per cent, a diagnosis of hyperthyroidism seemed justified at that time despite a basal metabolic rate of only plus 9. The pigmentation was also believed to be due to hyperthyroidism, since this does occur in a small percentage of thyrotoxic patients.³ In retrospect, we can see it is possible that her symptoms of weakness, anorexia, nausea and pigmentation, with a slightly elevated serum potassium (6.8 mEq.), were really the first signs of Addison's disease, despite a normal serum sodium level (141 mEq.). This impression is strengthened by the fact that the patient's symptoms did not subside until treatment with DCA and sodium chloride was started. If the symptoms present in December, 1951, were those of Addison's disease, then the patient also had hyperthyroidism at the same time, since her radioactive iodine uptake was 60 per cent. Authenticated cases of hyperthyroidism with a normal basal metabolic rate and a high I¹³¹ uptake have been noted.⁴ Actually, the basal metabolic rate of plus 9 may be a high figure, since hypometabolism is rather regularly found in Addison's disease. A high I¹³¹ uptake is occasionally seen in a patient who has had a very low iodine intake, this latter condition causing the thyroid gland to have a great affinity for iodine. A similar situation may exist in patients who have been treated with propylthiouracil without adjuvant use of iodine. Since our patient received potassium iodide with propylthiouracil for two weeks in 1947, and used iodized salt throughout the three year period ending September, 1950, during which she was on propylthiouracil therapy, we feel that the last-mentioned causes for high I¹³¹ uptake were, in all likelihood, not operative in this case. We think, therefore, that this patient had both hyperthyroidism and early Addison's disease at the time of her hospitalization in December, 1951. At the present time she shows the effect of a therapeutic dose of I¹³¹ and is clinically euthyroid.

We can offer no satisfactory explanation for the appearance of the three endocrine disturbances in this patient. The wide time span between the onset of diabetes mellitus and hyperthyroidism and the appearance of manifestations of Addison's disease makes it seem unlikely that a single causative factor for all three was present. The possibility that hyperthyroidism aggravated a low-grade adrenal insufficiency of undetermined cause must be considered.⁵ If thyrotoxicosis was responsible for secondary adrenal failure one would expect amelioration of the symptoms of adrenal insufficiency following the treatment with radioactive iodine. This did not occur in this case. We feel that the radioactive iodine could not have been a factor in the production of adrenal insufficiency since, as indicated by the findings presented in the previous paragraph, Addison's disease antedated the treatment with radioactive iodine.

SUMMARY

We have presented a case of a 52 year old woman in whom the simultaneous occurrence of diabetes mellitus, hyperthyroidism and Addison's disease was demonstrated.

BIBLIOGRAPHY

1. Rowntree, L. G., and Snell, A. M.: Clinical study of Addison's disease, Mayo Clinic Monographs, 1931, W. B. Saunders Co., Philadelphia.
2. Rhind, E. G. G., and Wilson, A.: Diabetes mellitus in Addison's disease, Lancet 2: 37-38 (July 12) 1941.
3. Williams, R. H.: Textbook of endocrinology, 1950, W. B. Saunders Co., Philadelphia.
4. Rossman, I.: Personal communication to the authors.
5. Gitman, L., Ant, M., and Jacobi, M.: Combined hyperthyroidism and adrenal cortical insufficiency: effect of iodine therapy: case report, Ann. Int. Med. 19: 507-514 (Sept.) 1943.

EDITORIAL

PREVENTION OF RHEUMATIC FEVER

THE following recommendations for the prevention of rheumatic fever are published by request of the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association.

Rheumatic fever is a recurrent disease which can be prevented. It is now generally agreed that both the initial and recurrent attacks of the disease are usually precipitated by infections with beta hemolytic streptococci. Therefore, the prevention of rheumatic fever and rheumatic heart disease depends upon the control of streptococcal illnesses. This may be successfully accomplished by (1) early and adequate treatment of streptococcal infections in all individuals and (2) prevention of streptococcal infections in rheumatic subjects.

I. Treatment of Streptococcal Infections

In the general population at least 3 per cent of untreated streptococcal infections are followed by rheumatic fever. Among certain individuals, especially those with previous rheumatic fever, the incidence is much higher. Adequate and early penicillin treatment, however, will prevent most attacks of rheumatic fever and eliminate streptococci from the throat.

A. Diagnosis of Streptococcal Infection

In most instances it is possible to recognize streptococcal infections by their clinical manifestations but laboratory tests may assist in establishing the diagnosis.

1. *Epidemiology:* The seasonal pattern and presence of similar cases in the community or household may be helpful. For example, streptococcal infections in the northern United States are most common from January through June. Likewise, a case of scarlet fever in one child would suggest that a sore throat in another has the same etiology.

2. Symptoms

- a. Sore throat—onset sudden, in the tonsillar area, not in the trachea.
- b. Headache—common.
- c. Fever—variable—but generally from 101° to 104° F.
- d. Abdominal pain—common, especially in children. Not too common in adults, but does occur.
- e. Nausea and vomiting—common, especially in children.
- f. These symptoms are usually *not* present:

- (1) Simple coryza
- (2) Cough
- (3) Hoarseness

3. *Signs*

- a. Red throat—frequently beefy red, but if seen early the redness may be mild.
- b. Exudate—usually present.
- c. Glands—swollen, tender tonsillar glands at angle of jaw.
- d. Rash—scarlatiniform (characteristic of scarlet fever—not common).
- e. Discharge—otitis media and sinusitis indicated by (serous or purulent) aural or nasal discharge are frequent complications of streptococcal pharyngitis.

4. *Laboratory*

- a. White blood count—generally over 12,000 and in children frequently over 20,000.
- b. Throat culture—positive for hemolytic streptococci.

5. *Therapeutic Response:* Almost without exception patients with streptococcal infections are vastly improved within 24 hours after penicillin has been started and the temperature normal, or nearly so.

This therapeutic response is characteristic and if it does not occur, the chances are much against the disease being due to hemolytic streptococci.

B. *Treatment of Streptococcal Infections*

In order to be effective, treatment should be started immediately when a streptococcal infection is suspected and continued for sufficient time to eradicate the streptococci from the throat.

Penicillin is the drug of choice for treating streptococcal infections.

Both the oral and the intramuscular routes of administration have been utilized successfully for penicillin therapy of streptococcal infections. Intramuscular injections have been proved to prevent rheumatic fever. The data on the value of oral penicillin as a preventive are less complete.

Oral administration in contrast to intramuscular administration has these advantages :

- (1) It is not as distasteful to many patients.
- (2) It requires fewer visits by the physician.

It has these disadvantages :

- (1) Larger amounts of penicillin must be used.
- (2) It is difficult to administer to vomiting or refractory children.
- (3) In some adults it gives rise to persistent diarrhea and pruritus ani.
- (4) It is difficult to be sure that treatment is continued for sufficient time and given in proper relation to meals to be effective.

1. Recommended Schedules

a. Intramuscular Penicillin

- (1) Children—one intramuscular injection of 300,000 units of procaine penicillin with aluminum monostearate in oil *every third day for three doses.*
- (2) Adults—one intramuscular injection of 600,000 units procaine penicillin in aluminum monostearate *every third day for three doses.*

(Note: Less preferable, but usually effective—two doses as above at three day intervals).

b. Oral Penicillin

- (1) First five days: 200,000 to 300,000 units one half to one hour before meals and at bedtime (total of 800,000 to 1.2 million units per day in 4 divided doses. Smaller amount children; larger amount adults).
- (2) Second five days: 200,000 to 250,000 units one half to one hour before meals (total 600,000 to 750,000 units per day in 3 divided doses).

Note: To be effective, therapy should be continued for the entire 10 days even though the temperature may return to normal and the patient may feel better within one or two days.

c. Combination of Intramuscular and Oral Penicillin

Therapy may be begun with one injection of penicillin (300,000 units procaine penicillin with aluminum monostearate in oil) and then, beginning three days after the injection, continued for an additional seven days with oral penicillin according to the schedule b (2) outlined above.

d. Other Medication

- (1) Aureomycin is less effective than penicillin in controlling streptococcal infection but is especially useful in those sensitive to penicillin.
Dosage: Total 10 mg. per pound of body weight in four divided doses daily for two days. Cut dose in half for remaining eight days of therapy.
- (2) New preparations of penicillin. These may be effective and even preferable to the treatment schedules outlined, but at present they have not had sufficient trial to warrant their recommendation.
- (3) Other antibiotics: At present there are inadequate data on their value.

- e. Not Recommended for Treatment
 - (1) Penicillin troches or lozenges.
 - (2) Penicillin followed by sulfonamides.
 - (3) Sulfonamide drugs

Note: Recurrences of streptococcal infection should be treated as primary attacks.

II. Prevention of Streptococcal Infections

A. General Rules for Prophylaxis

1. Who should be treated?

All individuals under the age of 18 who have had rheumatic fever or chorea and all those over this age who have had an attack within five years.

2. When should prophylactic treatment be initiated?

At the end of the second week of the attack of rheumatic fever or any time thereafter when the patient is first seen.* Prior to the start of prophylaxis, beta hemolytic streptococci should be eradicated by proper treatment of the patient.

(See methods of penicillin therapy recommended above.)

3. How long should prophylaxis be continued?

In children, at least to the age of 18; in all those above this age, for at least five years from their last attack.

4. Should prophylaxis be continued during the summer?

Yes.

B. Prophylactic Methods

1. Sulfadiazine

This drug has the advantage of being easy to administer, inexpensive and effective (other newer sulfonamides are probably equally effective). Although resistant streptococci have appeared during mass prophylaxis in the armed forces, this is rare in civilian populations.

a. Dosage—from 0.5 to 1.0 gm. taken each morning throughout the year. The smaller dose is to be used in children under 60 pounds.

b. *Toxic Reactions*—these are infrequent and are usually minor. However, in any patient being given prophylaxis with sulfonamides consider all rashes and sore throats as possible toxic reactions to the drug, especially if

* In patients receiving ACTH or cortisone, be cautious that other infections are not masked since the prophylactic dose is inadequate to treat such concurrent illnesses as pneumonia or meningitis.

they occur in the first eight weeks of prophylaxis. The chief toxic reactions are:

- (1) Skin eruptions
 - (a) Morbilliform—much like measles—continue drug with caution.
 - (b) Urticular—best discontinue treatment.
 - (c) Scarlatiniform—often associated with sore throat and fever. Unsafe to continue drug.
- (2) Blood reactions
 - (a) Leukopenia—discontinue if white blood count falls below 4,000 and polynuclear neutrophiles below 35 per cent because of possible agranulocytosis which is often associated with sore throat and a rash. Because of these reactions, weekly white counts are advisable for the first two months of prophylaxis. (The use of sulfonamides therapeutically for any reason in this period should be preceded by a white blood count.) The occurrence of agranulocytosis after eight weeks of continuous prophylaxis with sulfonamides is extremely rare.

2. Penicillin

Although experience with oral penicillin for the prophylaxis of rheumatic fever is more limited than that with the sulfonamides, the antibiotic promises to be a safe and effective prophylactic agent. Oral penicillin has the desirable characteristics of being bactericidal for hemolytic streptococci and of rarely producing serious toxic reactions. It has the disadvantages of being more costly than sulfadiazine and because of the need of giving it on an empty stomach, of being somewhat more difficult to administer.

Oral penicillin represents an alternative drug for rheumatic fever prophylaxis. It is especially important to use this agent for those who do not tolerate sulfadiazine.

a. Dosage

Although other routines of administration may prove satisfactory, the following schedules are suggested:

200,000 to 250,000 units two times daily is recommended. Since penicillin is best absorbed on an empty stomach, the time of administration should be one half to 1 hour before a meal or at bedtime. A single dose of 200,000 to 250,000 units before breakfast is less preferable.

b. Toxic reactions

- (1) Urticaria.
- (2) Reactions similar to serum sickness—they include fever and joint pains and may be mistaken for rheumatic fever.
- (3) Angioneurotic edema.

Although many individuals who have had reactions to penicillin can subsequently take the drug without trouble, it is safer not to

use penicillin, if the reaction has been severe and particularly if angioneurotic edema has occurred.

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BIBLIOGRAPHY

Thomas, C. B., France, R. and Reichman, F.: Prophylactic use of sulfonamide in patients susceptible to rheumatic fever, *J. A. M. A.* **116**: 537 (February 15) 1941.

Kuttner, A. G., and Reyersbach, G.: The prevention of streptococcal upper respiratory infections and rheumatic recurrences in rheumatic children by the prophylactic use of sulfanilamide, *J. Clin. Investigation* **22**: 77, 1943.

Baldwin, J. S.: Sulfadiazine prophylaxis in children and adolescents with inactive rheumatic fever, *J. Pediat.* **30**: 284, 1947.

Massell, B. F., Dow, J. W. and Jones, T. D.: Orally administered penicillin in patients with rheumatic fever, *J. A. M. A.* **138**: 1030, 1948.

Massell, B. F., Sturgis, G. P., Knobloch, J. D., Streeper, R. B., Hall, T. N. and Norcross, P.: Prevention of rheumatic fever by prompt penicillin therapy of hemolytic streptococcal respiratory infections: a progress report, *J. A. M. A.* **146**: 1469, 1951.

Denny, F. W., Wannamaker, L. W., Brink, W. R., Rammelkamp, C. H. and Guster, E. A.: Prevention of rheumatic fever. Treatment of the preceding streptococcal infection, *J. A. M. A.* **143**: 151, 1950.

Wannamaker L. W., Rammelkamp, C. H., Denny, F. W., Brink, W. R., Houser, H. B., Hahn, E. O. and Dingle, J. H.: Prophylaxis of acute rheumatic fever by treatment of the preceding streptococcal infection with various amounts of depot penicillin, *Am. J. Med.* **10**: 673, 1951.

Rantz, Lowell A.: The prevention of rheumatic fever, 66 pages, 1952, Charles C Thomas, Springfield, Ill.

REVIEWS

Great Adventures in Medicine. Edited by SAMUEL RAPPORt and HELEN WRIGHT. 874 pages; 14.5 × 21.5 cm. The Dial Press, New York. 1952. Price, \$5.00.

This volume is intended primarily for the lay public, but no one could be more misguided than the physician who lays it aside on that account. One might go so far as to say that it is a book which should be read by every member of the medical and nursing professions who has not already a wide and intimate acquaintance with medical literature, ancient and modern.

The book has been compiled at the end of five years of research by the editors. It is a collection of well selected medical writings, and, while not intended as a textbook of medical history, it offers a painless and exciting method of absorbing much historical lore. In its pages are distilled the spirits of each era of medicine.

All of its distillates are not from the pens of medical men. For example, the brutish and inebriate characters who were called nurses in early Victorian times are graphically portrayed in the famous pen picture of Sairey Gamp by Dickens. In effective contrast the story of Florence Nightingale follows.

The editors have divided their material into six parts. The first is brief and introductory. The remaining sections contain roughly chronological matter and are grouped under these self-explanatory titles: Ancient and Medieval Times; the Rebirth of Medicine; into Modern Times; the Turn of the Century—and Beyond; and Contemporary Medicine. The last section is probably of least value and interest to today's physician.

Apart from the virtues of the included selections themselves, this book will have served a useful purpose if it is a means of introducing unacquainted readers with the charming and worthwhile writings of such men as Conan Doyle, Hans Zinsser, Alan Guttmacher, and many others; if it encourages the medical man to dip more deeply into the essays of Oliver Wendell Holmes or the philosophical writings of Albert Schweitzer.

The book contains many famous original descriptions (or their translations) by such giants as Paracelsus, Paré, Sydenham, Hunter, Jenner, Laënnec, Leeuwenhoek, Lister, Pasteur, Bernard, Koch. Extracts from the writings of notable contemporaries such as Fleming, Dubos, Menninger, Cannon and Carrel are incorporated, and the wisdom of Hippocrates and Maimonides is not overlooked. The close relationship between magic and medicine is a prominent theme which recurs again and again in these pages.

The individual selections range from a few lines to over twenty pages. All in all this is a delightful anthology, admirable for either consecutive reading or intermittent delving, and of interest to anyone who is intimately or remotely concerned with the broad subject of medicine.

H. J. L. M.

The Clinical Application of Antibiotics: Penicillin. By M. E. FLOREY, M.D., Sir William Dunn School of Pathology, Oxford, England. 730 pages; 16 × 25.5 cm., Oxford University Press, London. 1952. Price, \$17.50.

This manuscript represents the third of a proposed four volume work concerned with the study of antibiotics, a subject termed by the publishers as a "new science." The parent monograph, a two volume set entitled *Antibiotics*, appeared in 1949 and dealt primarily with the chemical and pharmacological aspects of the then known antibiotics. The present book and an as yet unpublished fourth volume are intended to consider the clinical aspects, respectively, of penicillin and other antibiotics.

The motives in devoting an entire volume to a discussion of penicillin are quickly

established by Dr. Florey in the preface of this book. Penicillin was chosen not only because it was the first of the antibiotics shown to have systemic chemotherapeutic properties, but because the study lines which evolved from the work with the drug have become a guide to the investigation of the other antibiotics subsequently introduced into medicine.

The book is composed of 22 chapters separated into three large groups. The first deals with general considerations of penicillin and contains excellent basic sections concerned with toxic reactions and complications of therapy, types of penicillin preparations, dosage schedules and methods of administration. Many essential facts contributing to the clinical application of penicillin are collected in this initial portion of the volume and should be of especial interest to the physician who uses the drug extensively.

The second section is brief and devoted to penicillin therapy of diseases caused by specific organisms. The conditions considered vary from syphilis and anthrax to those produced by the hemolytic streptococcus.

The remaining portion of the book is concerned with penicillin as applied in the therapy of disease considered by system. Among those included are: diseases of the eye, nervous system and an interesting and informative chapter on the treatment of battle wounds.

An extensive bibliography composed of the majority of penicillin literature appearing up to late 1949 is included as are a large author and subject index. The primary bibliography is supplemented with additional references from the recent literature appearing either as footnotes or at the end of each chapter.

In general, the book is attractively arranged and quite readable. It is well written by one of the group of original workers in the antibiotic field and is enhanced by numerous pertinent charts and illustrations. However, in view of the rather exhaustive treatment given the subject, the volume would probably best serve as a reference source for the laboratory worker and interested clinician.

J. B. W.

Standard Values in Blood. (First fascicle of a Handbook of Biological Data, prepared under the direction of the Committee on the Handbook of Biological Data, American Institute of Biological Sciences, the National Research Council.) Edited by ERRETT C. ALBRITTON, A.B., M.D., Fry Professor of Physiology, The George Washington University. 199 pages; 21.5 × 28 cm. (paper-bound). W. B. Saunders Co., Philadelphia. 1952. Price, \$4.50.

Six hundred leading investigators in biology and in clinical medicine have collaborated in collecting the available physical, chemical and hematological data for the blood of animals belonging to various classes. The clinical data are unusually useful because they include variations from the usual normal values due to national, racial, geographic, sex and age factors, where these are known.

This volume should be very useful to anyone interested in biological and clinical investigation.

M. A. A.

Carbohydrate Metabolism: A Symposium on the Clinical and Biochemical Aspects of Carbohydrate Utilization in Health and Disease. Edited by VICTOR A. NAJJAR. 134 pages; 14 × 22 cm. The Johns Hopkins Press, Baltimore. 1952. Price, \$4.00.

This volume consists of eight papers and a summary, originally presented at a symposium on carbohydrate metabolism by a group of biochemists and pediatricians interested in this field. The purpose of the meeting was to present some of the newer information concerning carbohydrate metabolism and to interpret it for the benefit of the clinicians. The material presented by the biochemists was derived, for the

most part, from experiments using either purified enzyme systems or from in vitro studies using liver and muscle slices. The effect of hormones and electrolytes on these systems is described. The clinical papers stress the influence of three factors on carbohydrate metabolism, namely: (1) the enzymatic constitution, (2) the hormonal balance, and (3) the electrolyte pattern of the individual.

Dr. Anderson discusses three cases of glycogen storage disease, each of which might be interpreted as being the result of the congenital absence or abnormality of a single enzyme system. Dr. McQuarrie, in a section entitled "Spontaneous Hypoglycemia: Clinical and Metabolic Studies," outlines the various factors which cause hypoglycemia and points out a familial tendency toward hypoglycemosis in three families. Dr. Allen discusses some of the changes in carbohydrate metabolism that take place along with changes in electrolyte balance. The volume concludes with a summary written by Dr. Najjar.

Anyone interested in the biochemical aspects of carbohydrate metabolism not usually found in clinical journals would find this volume stimulating.

M. A. A.

Review of Physiological Chemistry. 3rd Ed. By HAROLD A. HARPER, Ph.D. 260 pages; 18 × 25.5 cm. (loose-leaf). University Medical Publishers, Palo Alto, California. 1951. Price, \$3.50.

This Review, now in its third edition, is written in outline form for medical students and for physicians preparing for state, national, or specialty boards. The author states that it is intended "to supplement the standard texts in biochemistry" and to "present the fundamentals of physiological chemistry with emphasis on the accepted facts and concepts of the subject." In the reviewer's opinion, this book admirably accomplishes the purposes for which it was written. Conciseness of presentation is emphasized and established principles favored over theoretical and controversial topics. The subject matter is well-selected, and a good balance has been drawn between the physical, organic, physiological, and clinical aspects of biochemistry. The 21 chapters contain the usual material found in standard texts on this subject. They include physical chemistry, carbohydrate, protein, and fat chemistry, vitamins, enzymes, blood and respiration, digestion, intermediary metabolism and nutrition, liver functions, kidney and urine chemistry, and the physiology and chemistry of the hormones. In fact, this outline could readily be expanded into a standard textbook because an extraordinarily large amount of scientific information has been condensed into its 260 pages. The student or physician who masters the subject matter in this outline will be well-fortified to meet most biochemical problems encountered in a modern medical or surgical practice. The chapters on enzymes, biological oxidations, and intermediary metabolism, subjects which are the object of intense research efforts and which are in a rapid state of development, appear especially complete, up-to-date, and well written. Dr. Harper has fortified his text with numerous well-selected structural formulae, 13 excellent figures, and 23 tables. Included is a detailed and helpful subject matter index. The type, paper and format are excellent.

E. G. S.

Tuberculosis of Bone and Joint. 2nd Ed. By G. R. GIRDLESTONE, Sometime Nuffield Professor of Orthopaedic Surgery in the University of Oxford; and E. W. SOMERVILLE, M.B., F.R.C.S. (Ed.), Orthopaedic Surgeon to the Wingfield-Morris Orthopaedic Hospital, Oxford. 314 pages; 17 × 25 cm. Oxford University Press, New York. 1952. Price, \$8.75.

This edition has been improved by revision generally and is an excellent review of tuberculosis of the bony system, stressing fundamental facts and analyses especially,

but also having sections relative to the newer thoughts and methods including antibiotics, but emphasizing caution regarding dependence upon them alone. The emphasis placed upon sound diagnostic procedures including careful history, principles of conservative therapy, and the merits of natural reactions is very heartening in this age of supposed short cuts, mechanical gadgets, etc. The illustrations are of good size and are clear and add much to the understanding of the text.

This book should be useful and of value to all medical practitioners and surgeons, but students and interns also would profit by reading it carefully. It reads easily and is an example of the excellent diction encountered in the literature of our English colleagues. Mr. Girdlestone was a known authority and student of surgical tuberculosis and his death is much regretted, but completion of his book by his associates will keep alive the soundness of his teaching of the principles of good patient-care.

A. F. V.

BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Die Angiographie zur Erkennung, Behandlung und Begutachtung peripherer Durchblutungsstörungen. By DR. MED. HABIL. H. W. PÄSSLER. 115 pages; 30.5 × 21 cm. (paper-bound). 1952. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, Inc., New York. Price, Kart. DM 29.70.

Biochemistry of Disease. 2nd Ed. By M. BODANSKY and O. BODANSKY. (Second Edition thoroughly revised and enlarged by OSCAR BODANSKY, M.D., Ph.D., Professor of Biochemistry, Sloan-Kettering Division, Cornell University Medical College, etc.) 1,208 pages; 23.5 × 15.5 cm. 1952. The Macmillan Company, New York. Price, \$12.00.

Blood Clotting and Allied Problems: Transactions of the Fifth Conference, January 21 and 22, 1952, New York, New York. Edited by JOSEPH E. FLYNN, M.D., Associate Professor of Pathology, College of Physicians and Surgeons, Columbia University, New York, New York. 368 pages; 23.5 × 16 cm. 1952. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$4.95.

Cardiographic Technique: A Manual for Cardiological Technicians. By S. L. BARROW, Member Royal Institute of Great Britain, and A. SCHOTT, M.D. (Heidelberg), M.R.C.S., Medical Officer in charge of Cardiographic Department, Queen Mary's Hospital for the East End (London). 156 pages; 22 × 14 cm. 1952. Grune & Stratton, New York. Price, \$5.50.

Dermatology: Essentials of Diagnosis and Treatment. (Complete revision of 3d Ed. *Dermatologic Therapy.*) By MARION B. SULZBERGER, M.D., Professor and Chairman, Department of Dermatology and Syphilology, New York University Post-Graduate Medical School, etc.; and JACK WOLF, M.D., Associate Professor of Clinical Dermatology and Syphilology, New York University Post-Graduate Medical School, etc. 592 pages; 23.5 × 15.5 cm. 1952. The Year Book Publishers, Chicago. Price, \$10.00.

Diseases of the Skin: A Manual for Students and Practitioners. First Compiled by the Late ROBERT W. MACKENNA, M.A., M.D., Ch.B. (Edin.). 5th Ed. by ROBERT M. B. MACKENNA, M.A., M.D. (Camb.), F.R.C.P. (Lond.), Physician-in-Charge of the Dermatological Dept. and Lecturer in Dermatology, St. Bartholomew's Hospital and Medical College, London, etc.; with a chapter concerning Radiology by I. G. WILLIAMS, F.R.C.S. (Eng.), D.M.R.E. (Camb.), F.F.R. (Gt.

B.), Director of the Dept. of Radiotherapy, St. Bartholomew's Hospital, London, etc. 611 pages; 24.5 × 16.5 cm. 1952. The Williams & Wilkins Company, Baltimore. Price, \$8.00.

Expert Committee on Public-Health Administration: First Report. World Health Organization Technical Report Series No. 55. 41 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 30 cents.

Grundriss der Elektrokymographie. By PRIV.-DOZ. DR. K. HECKMANN. 36 pages; 21 × 15 cm. (paper-bound). 1952. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, Inc., New York. Price, Kart. DM 6.60.

A Half Century's Progress Against Tuberculosis in New York City, 1900 to 1950. By GODIAS J. DROLET and ANTHONY M. LOWELL. 156 pages; 27.5 × 21.5 cm. (paper-bound). 1952. New York Tuberculosis and Health Association, New York. Limited supply available on request from public health officials and tuberculosis authorities, public or private.

Das Inselsystem des Pankreas. By HELMUT FERNER. 186 pages; 24.5 × 17.5 cm. 1952. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, Inc., New York. Price, Ganzl. DM 29.70.

Introduction to the Interpretation of the Electrocardiogram, with Sixty-one Plates Illustrating the More Important Deviations from the Normal, Selected from the Files of the Michael Reese Hospital. By LOUIS N. KATZ, A.M., M.D., Director, Cardiovascular Department, Medical Research Institute, and Attending Physician, Michael Reese Hospital, Chicago, etc.; RICHARD LANGENDORF, M.D., Research Associate, Cardiovascular Department, Medical Research Institute, and Associate Attending Physician in Medicine, Michael Reese Hospital, Chicago, etc.; and ALFRED PICK, M.D., Assistant Cardiographer and Research Associate, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago. 78 pages; 23 × 19 cm. (paper-bound). 1952. The University of Chicago Press, Chicago. Price, \$2.50.

Joint Expert Committee on the Physically Handicapped Child (convened by WHO with the participation of United Nations, ILO, and UNESCO): First Report. World Health Organization Technical Report Series No. 58. 26 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization, Geneva; Agents in U.S.A.: Columbia University Press, International Documents Service, New York. Price, 20 cents.

Metabolic Interrelations, with Special Reference to Calcium: Transactions of the Fourth Conference, New York, N. Y., January 7-8, 1952. Edited by EDWARD C. REIFENSTEIN, Jr., M.D., Director, Oklahoma Medical Research Institute and Hospital, Oklahoma City, Oklahoma; Editorial Assistant: SHIRLEY L. WELLS, M.S. 262 pages; 23.5 × 16 cm. 1952. Sponsored by Josiah Macy, Jr. Foundation, New York. Price, \$4.50.

Muscle Relaxation as an Aid to Psychotherapy. Physical Medicine Series, Vol. I. By GERALD GARMANY, B.Sc., M.B., Ch.B., M.R.C.P., D.P.M., Physician to Psychiatric Department, Westminster Hospital, etc.; General Editor: WILLIAM BEAUMONT, M.R.C.S., L.R.C.P., Director of Physical Medicine, Westminster Hospital, etc. 65 pages; 22.5 × 14.5 cm. 1952. The Actinic Press, Ltd., London. Price, 5/6 cloth ed., 3/6 paper ed.

Outlines of Internal Medicine. 7th Ed. Edited by C. J. WATSON, M.D., Head, Department of Medicine, University of Minnesota. 637 pages; 29 × 22 cm. 1952. William C. Brown Company, Dubuque, Iowa. Price, \$13.00.

The Physiologic Effects of Wounds: Surgery in World War II. Medical Department, United States Army. By THE BOARD FOR THE STUDY OF THE SEVERELY WOUNDED, NORTH AFRICAN-MEDITERRANEAN THEATER OF OPERATIONS. 376 pages; 25.5 × 17.5 cm. 1952. Office of the Surgeon General, Department of the Army, Washington, D. C. Price, \$3.50; available from Superintendent of Documents, Government Printing Office, Washington-25, D. C.

Problems of Consciousness: Transactions of the Third Conference, March 10 and 11, 1952, New York, New York. Edited by HAROLD A. ABRAMSON, M.D., Associate Physician for Allergy, The Mt. Sinai Hospital, New York, New York. 156 pages; 23.5 × 15.5 cm. 1952. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$3.25.

Side Effects of Drugs. By L. MEYLER, Consulting Physician at Groningen (Netherlands); translated by PH. VUIJSJE and MULHALL CORBET, Amsterdam. 268 pages; 23.5 × 15.5 cm. 1952. Elsevier Publishing Company, Houston. Price, \$5.50.

The Young Delinquent in His Social Setting: A Glasgow Study. By T. FERGUSON, Professor of Public Health and Social Medicine, University of Glasgow. 158 pages; 22.5 × 14 cm. 1952. Published for The Nuffield Foundation by Geoffrey Cumberlege, Oxford University Press, New York. Price, \$2.50.

COLLEGE NEWS NOTES

NOMINATIONS FOR A.C.P. ELECTIVE OFFICES, 1953-54

In accordance with provisions of the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1953-1954, are herewith announced to the Fellows and Masters of the College:

President-Elect Cyrus C. Sturgis, Ann Arbor, Mich.
First Vice President George F. Strong, Vancouver, B. C.
Second Vice President ... Alexander M. Burgess, Providence, R. I.
Third Vice President William C. Chaney, Memphis, Tenn.

Regular elections will take place at the 1953 Annual Session, Atlantic City, N. J., on April 16, 1953, the date of the Annual Business Meeting at Convention Hall, general headquarters.

The election of nominees shall be by the Fellows and Masters; the above nominations do not preclude other nominations made from the floor at the Business Meeting.

Nominations of members of the Board of Regents and Board of Governors will be presented at the Business Meeting, as provided in the By-Laws.

Respectfully submitted,

COMMITTEE ON NOMINATIONS

Walter L. Palmer, Chicago, Chairman
Paul F. Whitaker, Kinston
Ray F. Farquharson, Toronto
Leslie R. Kober, Phoenix
A. McGehee Harvey, Baltimore

NEW LIFE MEMBERS

The College is pleased to announce that the following Fellows have become Life Members of the American College of Physicians since the publication of the last list in the December, 1952, issue of this journal:

Dr. Ko-Kuei Chen, Indianapolis, Ind.
Dr. William C. Meredith, New Rochelle, N. Y.
Dr. Frank Princi, Cincinnati, Ohio
Dr. Hugh Albert Stout, Oklahoma City, Okla.
Dr. D. R. Bedford, Topeka, Kans.
Dr. Edward Massie, St. Louis, Mo.
Dr. Frederick Kellogg, Long Beach, Calif.
Dr. J. LeRoy Kimball, Salt Lake City, Utah
Dr. Robert S. Dyer, Louisville, Ky.
Dr. Karl W. Brimmer, Arlington, Va.

CANDIDATES FOR MEMBERSHIP, A.C.P.

Proposals for membership must be filed in the Executive Offices of the College sixty days in advance of action. Therefore, February 10, 1953 marks the closing date for receipt of proposals that may be acted upon at the 34th Annual Session of the College at Atlantic City, N. J., April 13-17.

NORTH CAROLINA REGIONAL MEETING

Regional Meetings have been conducted in North Carolina since 1929. The 1952 Regional Meeting was held at the Bowman Gray School of Medicine, Winston-Salem, December 4, 1952, under the Governorship of Elbert L. Persons, M.D., F.A.C.P. Dr. Manson Meads, F.A.C.P., was Chairman of the Committee on Arrangements, and Dr. Charles H. Armentrout, F.A.C.P., was Chairman of the Program Committee. The Scientific Program consisted of three formal papers, a clinical-pathological conference and a panel discussion on the Therapeutic Use of ACTH and Cortisone. The Reception and Dinner were held at the Oldtown Country Club. Dr. T. Grier Miller, F.A.C.P., Philadelphia, President of the College, was the chief speaker at the Banquet and Dr. Paul F. Whitaker, F.A.C.P., 3rd Vice President of the College, was a special guest. There were in attendance 46 Fellows, 26 Associates and 40 guests; for a total of 112.

Dr. Wingate M. Johnson, F.A.C.P., Professor of Clinical Medicine and Chief of the Private Diagnostic Clinic at Bowman Gray School of Medicine, was especially recognized during the Banquet. He was honored as the Founder-Editor of the North Carolina Medical Journal, now in its 13th year of publication. The Toastmaster said, in part, "This recognition is not for outstanding qualities as an internist, which he has, nor for his work in the development of a second 4-year Medical School in North Carolina, nor is it to be for his pioneer work in the establishment of Sections on General Practice at the meetings of the State Medical Society and the American Medical Association. As internists, and for the membership of the American College of Physicians, we wish to honor and show appreciation for Dr. Johnson's work as Medical Editor of the North Carolina Medical Journal. The very great value of a well edited monthly journal at the State level is obvious to all Fellows who were previously supplied with a volume of 'Annual Transactions,' and Dr. Wingate M. Johnson, F.A.C.P., of Winston-Salem, should be honored for his successful and continued accomplishments."

AMERICAN BOARD OF INTERNAL MEDICINE

Reexaminations—Written and Oral

1. Restrictions on the number of written examinations for which a candidate may apply have been waived. The interval between all written examinations will be not less than one year; however, the Executive Committee of the Board may, at its discretion, require a longer period, or may, for reasons it considers adequate, deny admission to reexamination. A fee of fifteen (\$15.00) dollars is required for each written reexamination. The fee is due upon application for reexamination.

2. Restrictions on the number of oral examinations for which a candidate may apply have been waived. The interval between all oral examinations will be not less than one year; however the Executive Committee of the Board may, in its discretion, require a longer period, or may, for reasons it considers adequate, deny admission to reexamination. A fee of forty (\$40.00) dollars is required for each oral examination. The fee is due upon application for reexamination.

3. This ruling does not make it mandatory for a candidate to repeat the examination within the specified time limit. Candidates may elect a longer interval in the case of both the written and oral examinations.

COMING EXAMINATIONS BY CERTIFYING BOARDS

The American Board of Internal Medicine, William A. Werrell, M.D., Executive Secretary-Treasurer, One West Main St., Madison, Wis.

Oral Examinations—New Orleans, La., Feb. 3-6, 1953
Boston, Mass., April 9-11, 1953
New York, N. Y., May, 1953 (exact dates not determined)

The closing date for acceptance of applications for the above orals was January 2, 1953, except for candidates in military or Naval service.

Oral Examinations—San Francisco, Calif., Sept. 21-23, 1953
Chicago, Ill., Nov. 20-Dec. 1-2, 1953

The closing date for acceptance of applications for San Francisco and Chicago is April 1, 1953.

Oral Examinations:

The Sub-specialties—Allergy, New York, N. Y., June 1953
Cardiovascular Disease, Philadelphia, Pa., April 7, 1953;
New York, N. Y., May 27, 1953
Gastro-enterology, Philadelphia, Pa., April 10, 11, 1953
Pulmonary Disease, Boston, Mass., April 8 or 9, 1953; Los Angeles, Calif., May, 1953

The closing date for acceptance of applications is February 1, 1953.

Written Examination—October 19, 1953

The closing date for acceptance is May 1, 1953.

The American Board of Pediatrics, John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Road, Rosemont, Pa.

Oral Examinations—Baltimore, Md., Feb. 20-22, 1953
Memphis, Tenn., March 27-29, 1953

The American Board of Physical Medicine and Rehabilitation, Robert L. Bennett, M.D., Secretary-Treasurer, 30 North Michigan Ave., Chicago 2, Ill.

Written and Oral Examinations—New York, N. Y., May 30-31, 1953

FIRST WORLD CONGRESS ON FERTILITY AND STERILITY

The First World Congress on Fertility and Sterility will be held on May 25-31, 1953, at the Henry Hudson Hotel, New York City. The Congress is sponsored by the International Fertility Association with the cooperation of the American Society for the Study of Sterility. Twenty-three scientific sessions are to be held, which will embrace the entire field of fertility and sterility, including sessions dealing with socio-economic factors, psychosomatic aspects, and artificial insemination. The sessions will be conducted in English, French and Spanish, with the use of earphones and simultaneous translations, as in the United Nations meetings. There will also be medical round table discussions, questions and answer periods, scientific exhibits and motion pictures. For further information address the Chairman of the Local Arrangement Committee, 1160 Fifth Avenue, New York 29, N. Y.

MISSISSIPPI VALLEY MEDICAL SOCIETY 1953 ESSAY CONTEST

The Thirteenth Annual Essay Contest of the Mississippi Valley Medical Society is being held in 1953. The Society is offering a cash prize of \$100.00, a gold medal, and a certificate of award for the best unpublished essay on any subject of general interest (including medical economics and education) and practical value to the general

practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents and citizens of the United States. The winner will be invited to present his contribution before the Eighteenth Annual Meeting of the Mississippi Valley Medical Society to be held in Springfield, Ill., Sept. 23, 24, 25, 1953, the Society reserving the exclusive right to first publish the essay in its official publication, the *Mississippi Valley Medical Journal* (incorporating the *Radiologic Review*). All contributions shall be typewritten in English in manuscript form, submitted in five copies, not to exceed 5000 words, and must be received not later than May 1, 1953.

Further details may be secured from Harold Swanberg, M.D., F.A.C.P., Secretary, Mississippi Valley Medical Society, 209-224, W. C. U. Building, Quincy, Illinois.

1953 MEETING OF THE AMERICAN PSYCHOSOMATIC SOCIETY

The American Psychosomatic Society has changed the dates of its Annual Meeting; instead of taking place in May, the Meeting will be held April 18-19, 1953, at Chalfonte-Haddon Hall Hotel in Atlantic City, N. J., immediately following the 34th Annual Session of the College.

UNIVERSITY OF PENNSYLVANIA INSTALS COLOR TV AS TEACHING MEDIUM

Television in natural color has been installed in the Hospital of the University of Pennsylvania and is being utilized currently as a new teaching medium for students of both the School of Medicine and the Graduate School of Medicine.

Four days a week surgical operations are being piped over a closed circuit from one of the operating rooms in the hospital surgery to a nearby classroom where students assemble before a receiving set to view surgical procedures and have them explained by experts.

The color video installation, according to the University's announcement, represents a gift of special apparatus contributed by friends of Dr. I. S. Ravdin, John Rhea Barton Professor of Surgery and Director of the Harrison Department of Surgical Research.

Present video activities at the University, which have extended over the past several months, have been conducted somewhat as experiments preliminary to the installation of TV equipment on an enlarged scale.

Eventually it is planned to install a large viewing screen of nearly stage-width proportions in Medical Alumni Hall, a medical amphitheatre recently completed as part of new medical construction presently under way at the University. Then as many as 350 student-viewers can be accommodated.

JOINT COMMISSION ON ACCREDITATION OF HOSPITALS HOLDS FORMAL CEREMONIES

The tremendous challenge to the Joint Commission on Accreditation of Hospitals in its assurance to the public of continued high standards of patient care was the theme of the formal ceremony conveying the Hospital Standardization Program from the American College of Surgeons to the Joint Commission on Saturday, December 6, 1952. The program was held in the John B. Murphy Auditorium, 50 East Erie Street, in Chicago.

Dr. Paul R. Hawley, The Director, American College of Surgeons, presided over the conveyance ceremony. Dr. Evarts A. Graham, Chairman, Board of Regents of the College of Surgeons, made the presentation and Dr. Gunnar Gundersen, Chairman, Board of Commissioners, Joint Commission on Accreditation of Hospitals, made the

acceptance speech. Dr. Edwin L. Crosby, Director of the Joint Commission, introduced the guest speaker, Senator Lister Hill of Alabama.

In his acceptance speech Dr. Gundersen stated that "Without question, our new responsibility ultimately affects the health and welfare of millions of people who each year pass through hospital doors in Canada and the United States."

Guest speaker Senator Hill, outlining the progress of hospitals in the last century, praised the program of accreditation. In speaking of the new responsibility of the Joint Commission, he emphasized the over-all importance of integrity in the final accounting to the public: "In no field of human endeavor is integrity as important as it is in the care of the sick and injured. Without integrity all else is meaningless. . . . In the acceptance of the program you, the members of the Joint Commission on Accreditation, must give an accounting to millions of patients of today and tomorrow. The lives of patients may well depend upon the standards you fix and enforce. A great trust is imposed in your hands. To that trust you will be faithful."

UNIVERSITY OF PENNSYLVANIA GRADUATE SCHOOL OF MEDICINE OFFERS SHORT COURSE IN PULMONARY PHYSIOLOGY AND PULMONARY FUNCTION TESTS

Dr. Julius H. Comroe, Jr., F.A.C.P., will act as Director of a Post-graduate Course entitled, "The Lungs: Clinical Physiology and Pulmonary Function Tests," under the auspices of the University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa., March 16-21, 1953. The Course is designed for internists, specialists in diseases of the chest, thoracic surgeons, anesthesiologists, radiologists, bronchologists or other practitioners or physiologists who wish to learn more of the fundamental concepts of pulmonary physiology and how these apply to clinical practice; also for physicians or physiologists who are or are about to be engaged, full time or part time, in studying patients with cardiopulmonary disease by physiologic technics or setting up cardiopulmonary function laboratories.

Full information may be obtained from the Dean, University of Pennsylvania Graduate School of Medicine, Philadelphia 4, Pa.

DR. C. J. WIGGERS, F.A.C.P., HONORED

Dr. Carl J. Wiggers, F.A.C.P., Head of the Department of Physiology at Western Reserve University School of Medicine, Cleveland, Ohio, is being honored by professional friends and associates as he prepares to retire after 35 years of service to the University and the medical profession. A life-size portrait of Dr. Wiggers has been unveiled at the School of Medicine, and will hang in the Millikin Room, used for faculty and professional meetings.

As an additional honor to the retiring professor, former students and friends have established at the School of Medicine a scholarship fund in the name of Dr. and Mrs. Wiggers. A book containing 180 letters and testimonials from many of the nation's leading medical men was presented at the time of the announcement of the scholarship. These letters refer to Dr. Wiggers as "one of the great men of Western Reserve University, and one of the men who has made Western Reserve great."

Dr. Wiggers will retire at the close of the current academic year, June, 1953, and will thereafter devote his full time to the editorship of the new journal, *Circulation Research*.

Dr. John W. Towey, F.A.C.P., Powers, Mich., has recently been named the 1952 recipient of the Dearholt Medal that is awarded by the Mississippi Valley Conference on Tuberculosis. Dr. Towey has been Medical Superintendent of the Pinecrest Sanatorium since its opening in 1922.

Dr. John W. Scott, F.A.C.P., Lexington, received the Distinguished Service Medal of the Kentucky State Medical Association at its annual meeting in Louisville. A former President of the Association, Dr. Scott is Physician-in-Chief at the Good Samaritan and St. Joseph Hospitals.

Dr. Roger M. Choisser, F.A.C.P., has recently been named the Outstanding Physician of the Year of the Medical Society of George Washington University School of Medicine, Washington, D. C. Dr. Choisser is Professor of Pathology at the University and Treasurer of the Washington Academy of Medicine.

Dr. J. Burns Amberson, Jr., F.A.C.P., New York, has recently been made President of the Trudeau Sanatorium, Saranac Lake, N. Y., succeeding Dr. Francis B. Trudeau, son of the founder, who has retired as President but who will continue as a trustee. Professor of Medicine at Columbia University College of Physicians and Surgeons and Visiting Physician in Charge of the Bellevue Hospital Chest Service, Dr. Amberson, formerly Vice President of the Sanatorium, is also former President of the American Trudeau Society and the New York Health and Tuberculosis Association.

At its Twentieth Anniversary in New York, the National Gastroenterological Association awarded gold keys to the past Presidents in recognition of their services. Among those so honored were: Dr. Anthony Bassler, F.A.C.P., New York; Dr. Horace W. Soper, F.A.C.P., St. Louis, and Dr. Clarence J. Tidmarsh, F.A.C.P., Montreal, Can.

Dr. John T. Thornton, F.A.C.P., Charlottesville, recently became a member of the Fifty Year Club of the Medical Society of Virginia. Dr. John T. T. Hundley, President of the Society, conferred the award of the certificate on Sept. 29, 1952.

Two members of the College have recently become editors of State medical journals. Dr. Lee Foster (Associate), Phoenix, is Editor-in-Chief of *Arizona Medicine*, and Dr. Rowland D. Goodman, II (Associate), East Orange, is Acting Editor of the *Journal of the Medical Society of New Jersey*.

Dr. Elston L. Belknap, Sr., F.A.C.P., Milwaukee, has recently been elected President of the Central States Society of Industrial Medicine and Surgery.

The American Therapeutic Society has recently elected Dr. Francis M. Pottenger, Jr., F.A.C.P., Monrovia, Calif., President. At the same annual meeting, Dr. Elbert L. Persons, Durham, A.C.P. Governor for North Carolina, and Dr. Ray W. Kissane, F.A.C.P., Columbus, Ohio, were named Vice Presidents. Dr. Howard Wakefield, F.A.C.P., Chicago, College Governor for Northern Illinois, was elected Treasurer.

The American Association of Blood Banks installed Dr. Israel Davidsohn, F.A.C.P., Chicago, as President at its recent annual meeting in Milwaukee.

Dr. Charles E. Watts, F.A.C.P., Seattle, has recently been installed as President of the Washington State Medical Association.

Meeting in Morgantown, the West Virginia Heart Association recently named Dr. Walter C. Swann, F.A.C.P., Huntington, President-Elect, and named Dr. William E. Bray, Jr. (Associate), also of Huntington, Secretary.

Dr. John A. Reed, F.A.C.P., Washington, D. C., was recently reelected Secretary of the American Diabetes Association. At the same time Dr. Reed was reappointed Chairman of the Association's Committee on Diabetes Detection and Education.

The American Association of Medical Clinics, at its Annual Session in Denver, Nov. 30-Dec. 1, 1952, elected Dr. Clair L. Stealy, F.A.C.P., San Diego, Calif., President. Dr. Wayne Gordon, F.A.C.P., Billings, Mont., was named Vice President and President-Elect, and Dr. Arthur H. Griep (Associate), Evansville, Ind., was made Secretary-Treasurer.

Dr. Norman Shure (Associate), Los Angeles, has been recently elected Secretary-Treasurer of the California Society of Allergy.

Holding its annual meeting in Baltimore, the Medical and Chirurgical Faculty of the State of Maryland recently elected as Vice Presidents Dr. Francis J. Geraghty, F.A.C.P., and Dr. R. Carmichael Tilghman, F.A.C.P., College Governor for Maryland, both of Baltimore.

Dr. Margil C. Carlisle, F.A.C.P., Waco, was elected Secretary of the Texas Pediatric Society at the recent annual meeting held in Dallas.

Dr. Hans H. Reese, F.A.C.P., Madison, Wis., and Dr. Roland P. Mackay, F.A.C.P., Chicago, were elected, respectively, President and President-Elect of the American Neurological Association at the yearly meeting of the society held in Atlantic City.

Meeting in Chicago, The American Society for the Study of Arteriosclerosis recently elected Dr. Nelson W. Barker, F.A.C.P., Rochester, Minn., President.

Dr. G. Lamar Arrington, F.A.C.P., Meridian, was recently installed as President of the Mississippi State Medical Association at its annual meeting in Jackson.

At the annual meeting of the Virginia Diabetes Association, held in Richmond in conjunction with the meeting of the State Medical Society, Sept. 28-Oct. 1, 1952, Dr. Collins D. Nofsinger, F.A.C.P., Roanoke, was elected President and Dr. Thomas S. Edwards (Associate), Charlottesville, was named a Vice President.

Dr. W. Barry Wood, Jr., F.A.C.P., St. Louis, recently delivered the series of Herzstein Medical Lectures at Stanford University School of Medicine, San Francisco. The theme of the lectures, "Cellular Immunology of Acute Bacterial Infections," included "Pathogenesis of Bacterial Pneumonia," "Surface Phagocytosis," and "Cytodynamics of Bacteremia."

Colonel Carl W. Tempel (MC), USA, F.A.C.P., Denver, was one of the collaborators on "Antimicrobial Therapy of Pulmonary Tuberculosis" that was presented in St. Louis, Dec. 27, 1952. The subject, part of the Symposium on Chemotherapy of

Tuberculosis, was part of the program of the 119th Meeting of the American Association for the Advancement of Science.

Dr. Louis A. Krause, F.A.C.P., Baltimore, former College Governor for Maryland, and Dr. O. Spurgeon English, F.A.C.P., Philadelphia, were members of the program of the First Annual Scientific Session of the Delaware Academy of General Practice, which met in Wilmington, Dec. 6, 1952. Their respective subjects were "Medicine and the Bible" and "Relation of Good Parental Care to Prevention of Psychosomatic Illness."

The First Annual Joseph H. Pratt Lecture, "Medicine's Number One Problem," was given by Dr. Howard A. Rusk, F.A.C.P., New York, Dec. 5, 1952. Dr. Elliott P. Joslin, F.A.C.P., and Dr. Heinrich G. Brugsch, F.A.C.P., Boston, were the discussers. The lecture was presented by the House Officers' Association of New England Center Hospital, Boston.

Dr. Edward W. Hayes, Sr., F.A.C.P., Monrovia, Calif., and Dr. Louis Mark, F.A.C.P., Columbus, Ohio, were two of the participants in a round-table luncheon discussion on "When Should Artificial Pneumothorax Be Terminated?" The discussion, sponsored by the Rocky Mountain Chapter, was part of the program of the interim session of the American College of Chest Physicians, held in Denver, Nov. 30-Dec. 1, 1952. As part of the same program, Dr. John F. Briggs, F.A.C.P., St. Paul, Minn., and Dr. Alvis E. Greer, F.A.C.P., Houston, Tex., were members of the group that discussed "Management of the Cardiac Patient." Dr. W. Bernard Yegge, F.A.C.P., Denver, acted as moderator.

Dr. Lester R. Dragstedt, F.A.C.P., Chicago, delivered the Fifth Annual Phi Delta Epsilon Lecture at the University of Toronto Faculty of Medicine on Nov. 17, 1952. His subject was "Physiology of Gastric Secretion and the Peptic Ulcer Problem."

Dr. Charles A. Poindexter, F.A.C.P., New York, and Dr. Robert S. Palmer, F.A.C.P., Boston, were among the participants in a Symposium on Hypertension, presented by the New Jersey Chapter of the American Academy of General Practice in Newark on Dec. 13, 1952. Their respective topics were "Diagnostic Aids" and "Therapy."

Under the Presidency of Dr. Robert H. Mitchell, F.A.C.P., Fort Worth, the Texas Rheumatism Association held its annual meeting Dec. 5, 1952, in Dallas. Dr. Charles L. Short, F.A.C.P., Boston, was the guest speaker; he discussed "Diagnosis and Treatment of Rheumatoid Arthritis" and "Recent Advances in the Treatment of Gouty Arthritis."

The Duke University School of Medicine, Durham, N. C., presented its annual Symposium on Advances in Therapy, Dec. 9-10, 1952. Speakers and their topics included: Dr. Cornelius P. Rhoads, F.A.C.P., New York, "Trends in Management of Neoplastic Disease"; Dr. Lewis Dexter, F.A.C.P., Boston, "Pathological Physiology of Mitral Stenosis and Its Surgical Implications"; Dr. Irving S. Wright, New York, A.C.P. Governor for Eastern New York, "Treatment of Myocardial Infarction," and Dr. Joseph J. Bunim, F.A.C.P., Chevy Chase, Md., "Prevention and Treatment of Rheumatic Fever."

Dr. Joseph F. Ross, F.A.C.P., Boston, presented the first in a series of lectures on "Recent Advances in Therapy" given in the Mount Sinai Hospital, New York. His talk delivered Dec. 10, 1952, was entitled "Contribution of Radioisotopes to the Control of Disease." Speakers yet to be heard include Dr. Richard H. Freyberg, F.A.C.P., New York, who will speak March 4 on "Critical Appraisal of the Newer Treatment for Rheumatoid Arthritis," and Dr. J. Burns Amberson, Jr., F.A.C.P., New York, who will discuss "Therapy of Tuberculosis" on March 18.

Dr. Henry H. Turner, F.A.C.P., and Dr. Edward C. Reifenstein, Jr., F.A.C.P., Oklahoma City, were among the speakers at the Fifth Annual Postgraduate Assembly in Endocrinology and Metabolism, held in Miami Beach, November 3-8, 1952. Dr. Turner spoke on "Pseudoendocrinopathies," "Ovarian Hypofunction Syndromes: A. Hypergonadotropic Syndromes; Ovarian Agenesis and Turner's Syndrome," "Ovarian Hypofunction Syndromes: C. Normogonadotropic Syndromes: Hypothalamic Amenorrhea"; while Dr. Reifenstein discussed: "Chemistry and Physiology of Parathyroids" and "Metabolic Bone Diseases; Relation to Endocrine Glands; Osteitis Fibrosa Generalisata, Osteomalacia, and Osteoporosis." They were also members of the faculty of a postgraduate course in endocrinology held in Havana, Cuba, Nov. 13-14, 1952 and sponsored by the College of Medicine, National University of Cuba.

Dr. Garfield G. Duncan, F.A.C.P., Philadelphia, and Dr. Francis J. Braceland, F.A.C.P., Hartford, Conn., will be among the nine guest lecturers who will address the Sixtieth Annual Meeting of the Oklahoma State Medical Association when the group convenes in Tulsa, April 13-15. Dr. Duncan, together with Dr. Oscar Swineford, Jr., F.A.C.P., Charlottesville, Va., was also one of the guests of the Medical Association of Puerto Rico at the annual meeting in Santurce, Dec. 10-14, 1952.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., will address the annual meeting of the American Association of the History of Medicine. His topic, "The Early Medical School Teaching Hospitals in the United States," will be presented April 12 at the Ohio State University Museum in Columbus.

A course in Occupational Health is currently being offered under the joint auspices of the University of Pennsylvania and the Chamber of Commerce of Greater Philadelphia. Dr. Lemuel C. McGee, Wilmington, A.C.P. Governor for Delaware, delivered one of the opening lectures Feb. 18 at the University of Pennsylvania School of Medicine, his subject being "Industrial Medical Services from the Viewpoint of the Industrial Physician." Additional speakers and their topics will include: Mar. 11—Dr. John H. Foulger, F.A.C.P., Wilmington, "Industrial Solvents"; Mar. 18—Dr. William Dunbar (Associate), Philadelphia, "Evaluation of the Employability of Cardiac Patients," and Dr. Louis B. Laplace, F.A.C.P., Philadelphia, "Factors Determining Suitable Work for Cardiac Patients"; April 8—Dr. Robert Clinton Page, F.A.C.P., New York, "The Present Philosophy of Industrial Medical Services," and Dr. McGee, "Pitfalls in the Diagnosis of Occupational Disease"; April 22—Eugene P. Pendergrass, F.A.C.P., Philadelphia, "The Radiologic Aspects of Dust Diseases of the Lung."

Dr. Isadore Rudnikoff, F.A.C.P., Yonkers, N. Y., has been appointed Director of Medicine at the Yonkers General Hospital as of January 1, 1953.

Dr. Irving S. Wright, F.A.C.P., New York City, President of the American Heart Association, was guest of honor and speaker at the regular dinner meeting of the Houston (Tex.) Society of Internal Medicine on November 7, 1952. Dr. Paul V. Ledbetter, F.A.C.P., was general chairman.

Dr. Kenneth L. Benfer (Associate), York, Pa., sailed on December 29, 1952, for North Nigeria, British West Africa, where he will spend several months assisting in the Department of Medicine of a mission hospital. About September 1, 1953, he will proceed to England to spend three months in postgraduate work in the laboratories and associated departments of Sir Lionel Whitby, Regius Professor of Physic, University of Cambridge. Thereafter Dr. Benfer will return to his practice in York.

Dr. Arthur C. DeGraff, F.A.C.P., New York, recently resigned from the Board of Trustees of the United States Pharmacopeial Convention to accept an appointment to the Committee on Revision. Dr. DeGraff succeeds the late Dr. William T. Salter, F.A.C.P.

Dr. William Kaufman (Associate), Bridgeport, Conn., has been appointed to the Editorial Board of the *International Archives of Allergy and Immunology*. In December he read a paper entitled "Some Emotional Uses of Foods" at the meeting of the American Association for the Advancement of Science in St. Louis.

Dr. Jerome Weiss (Associate), New York, has recently been promoted to Assistant Visiting Physician at the Morrisania City Hospital.

The Colorado Foundation for Research in Tuberculosis proposes to honor the late Dr. Gerald Bertram Webb, F.A.C.P., by constructing a permanent building to be known as the "Gerald B. Webb Memorial." The Memorial, where continued research will be conducted in tuberculosis, will be located in Denver adjacent to the School of Medicine Building of the University of Colorado.

CORRECTION

In the News Notes section of the December, 1952, issue of this journal, it was stated that Dr. Wyndham B. Blanton, F.A.C.P., Richmond, had been appointed Assistant to the Dean, Medical College of Virginia. This should have referred to Dr. Wyndham B. Blanton, Jr., who is not a Fellow of the American College of Physicians.

Dr. H. P. Close, F.A.C.P., recently Chief of Medical Service at the Veterans Administration Hospital at Coatesville, Pa., has been appointed Chief of the Medical Service of the new Veterans Administration Hospital, now opened, in Philadelphia, Pa.

OBITUARIES

DR. ABRAHAM EZRA JAFFIN

Dr. Abraham Ezra Jaffin, F.A.C.P., age 68, died of cancer on November 25, 1952, at the Jersey City Medical Center. Born in Lithuania, he had made his home in Jersey City since the age of three. He was graduated in 1905 from Columbia University College of Physicians and Surgeons. He was an Interne and Resident Physician at Mount Sinai Hospital in New York and began practice in Jersey City in 1909.

Dr. Jaffin served on the staffs of the Jersey City Medical Center, the Berthold S. Pollak Hospital for Chest Diseases and the Bayonne Hospital and Dispensary. He was a former President of the Hudson County Medical Society and of the New Jersey Tuberculosis League.

During World War I, Dr. Jaffin was a First Lieutenant with the U. S. Army Medical Corps. He held membership in the American Medical Association, the National Tuberculosis Association and the American Heart Association. He was a Fellow of the New York Academy of Medicine as well as of the Academy of Medicine of Northern New Jersey. He became a Fellow of the American College of Physicians in 1922.

Dr. Jaffin, throughout his entire medical life, viewed his profession as an art. He furthered his medical knowledge in Vienna, Austria; and up to a short time before his last illness, he still took postgraduate courses.

He was truly the doctor's doctor, for many physicians and members of their families were the recipients of his professional skill and unfailing devotion. He will be greatly missed by the community and by his countless friends.

EDWARD C. KLEIN, JR., M.D., F.A.C.P.,
Governor for New Jersey

DR. FRANK NORMAN WILSON

Dr. Frank Norman Wilson, F.A.C.P., was born in Livonia Township near Detroit, Michigan, on November 19, 1890, the only child of Norman Wilson and Mary Holtz. His early school work was taken in a country school and his high school training in the Western High School in Detroit. Even before he came to Ann Arbor in 1907 for study at the University of Michigan, he was keenly interested in the natural sciences, and it is not surprising that he went on into medical work and graduated from the University of Michigan Medical School in 1913.

Soon after graduation, Dr. Wilson began his work in the Department of Internal Medicine in University Hospital. He was fortunate to have as his chief the late Dr. A. W. Hewlett, who encouraged him in research activities and initiated his work in the then very poorly developed field of electrocardiography. Many times in later years Dr. Wilson expressed his debt to and deep regard for Dr. Hewlett. Several papers were published by Dr. Wilson during the period from 1913 to 1916, and even in these early publications one finds the clarity of style and the fundamental approach to problems that characterize to such a high degree his later work.

When Dr. Hewlett left Ann Arbor to take a position at Stanford University in 1916, Dr. Wilson went to Washington University in St. Louis, but in 1917 entered military service and was assigned to work at Colchester, England, with Sir Thomas Lewis on a study of effort syndrome in soldiers. Drs. Samuel A. Levine, Marcus A. Rothschild, Rufus Morrison, William St. Lawrence, Thomas Cotton and Ross Jamieson were also members of this group of physicians, and close and enduring friendships between Dr. Wilson and these men began during this period. Sir Thomas and Dr. Wilson became close friends, and the former's interest in birds and the photography of birds on their nests was imparted to his associate at this time. This

hobby continued to give pleasure and satisfaction to Dr. Wilson during the rest of his life.

Following discharge from the Army in 1919, Dr. Wilson returned to St. Louis, but in 1921 was recalled to Ann Arbor, where he worked until his activities were interrupted by illness in 1948.

Dr. Wilson wrote over 100 scientific papers, including a monograph and articles that appeared in several books. Most of his work was devoted to the electrocardiogram, and it is fair to say that he contributed far more to our understanding of these records and the development of electrocardiography as an important clinical science than any other physician. Much of our current knowledge of the ventricular complex, particularly in connection with bundle branch block and myocardial infarction, is based on clinical and experimental studies done several years ago by Dr. Wilson, and the central terminal arrangement he devised over twenty years ago is the circuit now universally used in the registration of "unipolar electrocardiograms." The importance of a number of Dr. Wilson's best contributions has not been appreciated until long after their completion, often at a time when he was fully occupied with quite different work. He was never much interested in collecting and re-writing old material for publication and preferred to use his energy in new fields. This is one reason why he never wrote a book on the electrocardiogram.

During the many years that Dr. Wilson worked in the Heart Station and his reputation increased, his duties multiplied. His skill as a clinician led numerous patients, including many physicians, to consult him with real or fancied cardiac complaints. He was not always able to settle the problem at hand with certainty, but he always took the time required to obtain a full history and to do a detailed cardiac examination. When his workup, of which the electrocardiogram often played a very small part, was finished he talked to the patient, often at great length. Whatever his verdict and advice, patients felt better after the visit.

Recent graduates from the Medical School have seen relatively little of Dr. Wilson, since circumstances limited his participation in undergraduate teaching work for a number of years prior to his retirement due to illness in 1948. His yearly postgraduate course in electrocardiography, however, attracted physicians in increasing numbers to Ann Arbor, and his lectures remain as a treasured memory to hundreds of doctors. Although facilities were not ideal for such instruction, many physicians from all over the world have spent varying periods of time studying electrocardiography in the Heart Station. In this informal instruction, as in all of his teaching, Dr. Wilson emphasized the importance of not over-reading electrocardiograms and using them in close correlation with clinical data.

Many honors came to Dr. Wilson during his last years. Issues of *Circulation* (July 1950) and the *American Heart Journal* (November 1950) containing suitable appreciations were dedicated to him, and the Gold Heart Medal of the American Heart Association was given to him in June 1951. These tributes came at a time when he was on sick leave, and they were greatly appreciated. One of Dr. Wilson's greatest pleasures was an active life out-of-doors, and it is not surprising that he became discouraged at times during the long final period of physical inactivity. In spite of this situation, Dr. Wilson continued his active study of electrocardiographic problems, and he was always willing to help in the research activities of the Heart Station. His death, due to coronary thrombosis on September 11, 1952, is not only a great personal loss to his many friends and associates but marks the passing of one of the greatest physicians and scientists of modern times.

FRANKLIN D. JOHNSTON, M.D., F.A.C.P.

ABSTRACT OF MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

NOVEMBER 16, 1952

The regular autumn meeting of the Board of Regents of the American College of Physicians was held at the College Headquarters in Philadelphia, Pa., Sunday, November 16, 1952, beginning at 9:45 a.m. President T. Grier Miller presided, and Mr. E. R. Loveland acted as Secretary, with the following in attendance:

T. Grier Miller	<i>President</i>
Walter B. Martin	<i>First Vice President</i>
Charles F. Moffatt	<i>Second Vice President</i>
Paul F. Whitaker	<i>Third Vice President</i>
William D. Stroud	<i>Treasurer</i>
Richard A. Kern	<i>Secretary-General</i>
A. B. Brower	
George H. Lathrop	
Cyrus C. Sturgis	
Asa L. Lincoln	
J. Owsley Manier	
Walter L. Palmer	
Wallace M. Yater	
Edward L. Bortz	
Herbert K. Detweiler	
Harold H. Jones	
Howard P. Lewis	
Dwight L. Wilbur	
E. R. Loveland	<i>Executive Secretary</i>
Thomas M. McMillan	<i>Chairman, Committee on Postgraduate Courses</i>
George Morris Pierpol	<i>Chairman, Committee on Credentials</i>
Hilton S. Read	<i>General Chairman, 34th Annual Session</i>

In view of the fact that the Minutes of the preceding meetings of the Board of Regents, held at Cleveland during April, 1952, had been published in the "Annals of Internal Medicine" reading thereof was dispensed with by formal resolution.

The Secretary, Mr. Loveland, presented the following communications:

- (1) Report of the gift of a beautiful silk American Flag to the College by Mr. William S. Brede, Minneapolis, the College Exhibit Contractor;
- (2) A report that Dr. José J. Centurión, College Governor for Cuba, on appointment by the President, served as the official College representative to the First International Congress on Public Health at Havana, Cuba, Sept. 25-Oct. 1, 1952;
- (3) A report that Dr. Edward L. Bortz, Regent, was the official College delegate, on appointment by the President, to the Centennial Meeting of the American Pharmaceutical Association at Philadelphia, August 20, 1952. A commemorative scroll was presented on behalf of the College, as was done by many other organizations;
- (4) A report that Dr. Howard Wakefield, College Governor for Northern Illinois, was the official College representative at the Twenty-fifth Anniversary celebration of the University of Chicago School of Medicine on October 3, 1952;

- (5) A report that Dr. Herbert K. Detweiler, Regent of the College, was the official College representative at the Annual Meeting of the Royal College of Physicians and Surgeons of Canada at Toronto, Ont., October 3-4, 1952;
- (6) A report that President T. Grier Miller attended as the official of the College the 38th Annual Clinical Congress of the American College of Surgeons in New York, N. Y., September 22, 1952;
- (7) A report that Dr. Chester S. Keefer, College Governor for Massachusetts, represented the College officially at the Centennial Celebration of Tufts College at Boston, October 11, 1952;
- (8) A report that Dr. J. Owsley Manier, Regent of the College, was its official representative at the Presidential Inauguration at Meharry Medical College, October 20, 1952;
- (9) A report from Dr. LeRoy H. Sloan, College Commissioner and member of the Advisory Committee of the Joint Commission on Accreditation of Hospitals, stating that Dr. Edwin L. Crosby, the new Director, is already engaged in the preliminary surveys, that the Commission is housed at 660 Rush Street, Chicago, that it was planned shortly to have a formal Convocation at which the American College of Surgeons would turn over the hospital survey records to the Commission and that the next official meeting of the Commission would be held in December;
- (10) A report from Dr. LeRoy H. Sloan, Chairman of the Conference Committee on Graduate Training in Medicine, stating that a pilot survey in Michigan will shortly be activated and consideration will be given to alterations in the requirements for residencies in Internal Medicine. The pilot survey of the residencies in Internal Medicine in Michigan will be conducted on the pattern of the one completed in Illinois;
- (11) A communication from "CARE" concerning the College continuing seven complimentary subscriptions to the ANNALS OF INTERNAL MEDICINE to certain medical institutions in Austria, Germany, Finland and Greece.

On motion moved by Dr. Cyrus C. Sturgis, seconded by Dr. Howard P. Lewis, and unanimously carried, the Secretary was instructed to write a letter of appreciation for the gift of the American Flag by Mr. William S. Brede.

On motion by Dr. Howard P. Lewis, seconded by Dr. A. B. Brower, and carried, the continuance of the seven complimentary subscriptions on behalf of "CARE" was approved.

President Miller then called for the report of the Secretary-General, Dr. Richard A. Kern.

DR. RICHARD A. KERN: "Mr. President, the deaths since the last meeting of this Board total 48 Fellows and 4 Associates, as follows: (Read list of deceased, following which the Regents observed a moment of silence in their memory)."

DR. KERN (continuing): "Additional Life Members since the last meeting of this Board include the following 30 Fellows, making a grand total of 1,053, of whom 108 are deceased, leaving a balance of 945: (Read list of names for recording in the Minutes)."

PRESIDENT MILLER: "We now come to new business and reports. The first item is the consideration of the appointment of a Governor for British Columbia."

SECRETARY LOVELAND: "For the past several years we have had one Governor for the combined Provinces of Alberta and British Columbia. Each Province has twenty members, but the area covered is quite great. We have received recommendations from one former Regent, Dr. George F. Strong, and from the current Governor, Dr. John W. Scott, that the Province of British Columbia be separated from the Province of Alberta and a separate and additional Governor elected for British Columbia. The

By-Laws provide 'Upon recommendation of the Board of Regents and the affirmative action of the College at the Annual Business Meeting the number of Governors may be increased by the election of an additional member or members to represent a state or territory or other geographical unit in which on account of extent or population it is desirable to have additional members for the better conduct of the work of the Board of Governors.'

"There is another related matter that might receive consideration at the same time, namely, the Chairman of the Committee on Nominations finds that the total College membership in Nevada consists of four Fellows. One of these, the present Governor, is no longer eligible for further service on the Board of Governors. Another is in the Veterans Administration Service and not eligible for the Governorship. Until that state has a larger fellowship in the College, it may be more appropriate to add it to the State of Arizona or to Northern California, allowing our present Governors in one of those States to function also for Nevada."

. . . After general discussion, it was moved by Dr. Charles F. Moffatt, seconded by Dr Herbert K. Detweiler, put and carried, that the Regents approve and recommend for adoption at the next Annual Business Meeting of the College the establishment of the Province of British Columbia as an independent geographical unit with its own Governor. . . .

Dr. WALTER L. PALMER: "The Committee wonders if it really is desirable or necessary to have a Governor in Nevada? It seems to the Committee, by virtue of the type of situation, it might be better to join Nevada with Arizona or Northern California."

. . . After general discussion, on motion of Dr. A. B. Brower, seconded by Dr. Dwight L. Wilbur, and carried, it was

RESOLVED, that the Board of Regents shall recommend to the Fellows at the next Annual Business Meeting that Nevada be associated with Northern California and be under the Governorship of that region. . . .

President Miller introduced a discussion of the California Society of Internal Medicine. The Secretary then reviewed various letters he had received from Dr. W. Philip Corr, F.A.C.P., President of the Society, the letters describing the activities and objectives of the said Society. The California Society of Internal Medicine was started in 1946, its primary purpose being to represent the economic interest of the internist. It has held a meeting of one day's duration each year and has represented in addition to the economic interest of internists, scientific and social features. Representatives of the Society have stated that they in no way feel that this new Society will compete with the American College of Physicians, nor has it been organized for that purpose. It is made up of competent internists of the State of California for political and economic purposes. It has set up fee schedules for insurance reports, compensation cases, consultation fees, and for the purpose of bargaining with insurance companies and organizations, such as the California Physicians' Service. No action was taken by the College relating to this new Society.

The following report was received from Dr. Alex M. Burgess concerning the Joint Commission on the Accreditation of Hospitals:

"Mr. President and Members of the Board of Regents:

"The American College of Physicians, as a member organization of the Joint Commission on Accreditation of Hospitals, is represented by the following three Commissioners: Dr. LeRoy H. Sloan, Dr. William S. Middleton and Dr. Alex M. Burgess. Dr. Sloan is Vice Chairman and a member of the Advisory Committee. Illness prevents Dr. Sloan from preparing and presenting this report.

"The organization of the Joint Commission has been described in previous reports. The last meeting of the Commission was held in Chicago, June 13, 1952, and 'Abridged Minutes' of this meeting were published in the October Issue of the ANNALS OF

INTERNAL MEDICINE. Certain actions taken at that time are worth repeating: Of these the most important is the announcement that Dr. Edwin L. Crosby had accepted the appointment as Director of the Commission. Dr. Crosby has established the office at 660 N. Rush Street, Chicago. Miss Martha Johnson, R.N., M.P.H., has been employed as Assistant to the Director.

"An orientation course for inspectors is to be opened on November 17, 1952, and will last for one or two weeks, as is found advisable. It is being held 'in order that the philosophy and procedure of inspection might follow a similar pattern, regardless of the member organization with which the inspector is affiliated.' The inspectors are those which have been carrying our inspections for the various member organizations, plus a few who have been newly recruited. It was noted that the 'inspectors now employed by the American College of Surgeons be requested to assist Dr. Crosby in conducting the course.' The College of Physicians, not having employed inspectors, will not contribute to this phase of the work.

"Other actions of this meeting that are of interest are the vote to reprint and distribute the By-Laws, and the vote to authorize the Director to publish a Bulletin. It was also decided that, during the period between the organization of the Commission and the beginning of the field work of its inspectors in 1953, approval of hospitals already accredited by the College of Surgeons would be given on analysis of inspection reports, or without inspection 'upon unanimous recommendation of the Advisory Committee.'

"The Advisory Committee met in Chicago on September 10, 1952. At this meeting Dr. Edwin L. Crosby, Mr. George Bugbee and Doctors Hawley and Sloan were present. Dr. E. H. Leveroos was also present, representing Dr. George F. Lull. It was decided to send copies of the By-Laws of the Commission to all listed American and Canadian hospitals. It was announced that a convocation will be held December 6, 1952, and that Senator Lister Hill, of Alabama, will be invited to deliver the principal address.

"As regards hospital surveys, the following facts were announced: The American Medical Association employs eight surveyors, who have been inspecting hospitals for internships and/or residencies, and these surveyors could be responsible for about 350 hospitals a year. The College of Surgeons would utilize four surveyors who would, it was thought, cover about 200 a year. The remainder of the hospitals needing inspection would be inspected by the five surveyors of the American Hospital Association. One of the above might be assigned to Canada. The inspections will begin on, or before, January 1, 1953. Assignments will be made by the Director after consultation with the members of the Advisory Committee. The orientation course for all surveyors, as previously announced, will begin on November 17, 1952. Reports of surveys will be processed and evaluated by the Director's office, submitted for review to the Advisory Committee, and presented to the Board of Commissioners. It is intended that the Advisory Committee shall meet once a month in the office of the Director. No certificates will be issued until surveys by the Joint Commission on Accreditation of Hospitals have been completed.

"The next meeting of the Commission is scheduled for December 7, 1952, at Chicago, on the day after the convocation."

PRESIDENT MILLER: "No action is required. If there are no comments, we will receive the report from Dr. Walter L. Palmer, Chairman of the American Board of Internal Medicine."

DR. PALMER: "Mr. President, the Board of Internal Medicine this year gave a written examination to 1,574 candidates. The failure rate has not yet been determined. This is the third year in which written examinations have been given to between 1,500 and 1,700 candidates. In four oral examinations, the Board has passed,

in 1952, 532 candidates. We have given examinations two days last week in Washington and will give them two days here in Philadelphia, tomorrow and Tuesday, and shall probably certify about 200 more, so that this year a few over 700 will be certified. That again has been the approximate rate for the past three years. The failure rate in the oral examinations this year has been remarkably consistent—31.2%, 31.4%, 32.2% and 33.1%—for the four examinations held thus far.

"The total number certified in Internal Medicine to November 1, 1952, is 7,847. Of this number, 1,945 were certified without examination. That means then that in the fifteen or sixteen years since the Board was organized it has certified almost 6,000 individuals by examination. The American Board of Internal Medicine examines more candidates per year than any other Board. It fails more candidates per year and it certifies more candidates per year than any other Board.

"In the sub-specialty board, we certified, during 1952, 14 in Cardiovascular Disease, 2 in Allergy, 1 in Gastro-enterology. That makes thus far a total of 135 in Cardiovascular Disease; 192 in Gastro-enterology, and 296 in Pulmonary Disease.

"Dr. Ray F. Farquharson has been elected to the Board, succeeding Dr. Marion A. Blankenhorn, who was not eligible for re-election. Dr. Hugh Butt, Dr. Howard P. Lewis and Dr. Thomas Findley have also been elected to the Board."

PRESIDENT MILLER: "Thank you, Dr. Palmer. May we now have the report of the Executive Secretary, Mr. E. R. Loveland?"

SECRETARY LOVELAND: "This report is supplementary to information which will be revealed through the reports of various Committees. However, I would like to bring out a few of the highlights of the past year's operations.

"New Elections:

	<i>Fellows</i>	<i>Associates</i>
Annual Session Report: 1949-50	300 (31 direct)	473
1950-51	327 (13 direct)	400
1951-52	296 (17 direct)	443

"I would like to point out also that the number of candidates considered at the present meeting is not materially different from the number a year ago, except that there are 43 less candidates for Fellowship and but 10 more candidates for Associateship:

	<i>Fellow Candidates</i>	<i>Associate Candidates</i>	<i>Total</i>
November, 1951	179	306	485
November, 1952	136	316	452

Resignations and Dropped Members: For the current meeting there is but one resignation (an Associate) and none to be dropped. The explanation of this, in comparison with recent years, is the change in the By-Laws extending the Associate term to ten years. Most of the resignations heretofore have been of Associates who foresaw they were not going to qualify for Fellowship within the maximal period allowed.

Regional Meetings: During the calendar year 1952, 24 have been scheduled, one more than for like period in 1951, with a somewhat increased attendance. Several additional Regional Meetings are already scheduled for 1953. A list of the 1952 meetings and of the 1953 meetings now scheduled has been duplicated for your information. One of the finest multi-state type meetings was held for the Southeastern States and Cuba at Havana, November 7-8, upon which President Miller may wish to comment, due to its probable far-reaching influence on a better relationship between the Cuba profession and ours of the United States.

"Postgraduate Courses: During 1952, 16 courses have been conducted and while the registration is not yet complete for all the courses, it is believed the total participation will be between eleven and twelve hundred physicians. This activity still continues to be eminently successful, due to the work of the Chairman of the Committee and the excellent cooperation of institutions and directors.

"Annals of Internal Medicine: Circulation has increased approximately 5% over last year; volume of advertising has slightly decreased, but net income has increased more than \$9,000.00 over the previous year; however, we face a further increase of 5% in all publication costs, beginning November 1, 1952 and 7% beginning November 1, 1953, due to new Union contracts in our printer's plant.

"Directory: In 1952 we merely published a Supplement to the 1951 Directory, the Supplement costing about \$1,500.00. 1953 is the year for the revision of the Directory and its re-publication. This entails an enormous amount of the most careful painstaking work, more than our present staff can accomplish. This Directory is of primary importance to the College, to the membership and to institutions and Services all over the country, and in my opinion is justified in every way. It is assumed that the Board of Regents desires the new Directory to be published under the same conditions as the 1951 Directory, namely, that no charge be made to Life Members, but that all other members be enabled to subscribe at a pre-publication reduced price of \$4.00; the regular sale price of the Directory after publication should be \$6.00 (\$1.00 increase over the post-publication price of 1951). This will not cover the full cost of the Directory, but will reduce its net cost to possibly \$2,000.00, whereas the gross cost will probably be \$15,000.00 to \$16,000.00.

"Thirty-Third Annual Session, Cleveland, Ohio: Cleveland attracted a gross registration of 4,436, as compared with 3,259 the year before at St. Louis. Of this number, however, there were only 3,191 physicians. There were 684 visiting women and the rest were non-physicians, medical students, exhibitors, etc. In 1949 at New York, our largest meeting, we had a gross registration of 5,627, of whom 3,957 were physicians. The Cleveland Session cost a total of \$43,426.00, but that was offset by a net income of \$41,934.00 from Exhibits and Guest Fees, so that the net cost of the meeting was \$1,492.00. The year previous, 1951 at St. Louis, the gross cost of the meeting was \$11,000.00 less and the income from Exhibits and Guest Fees more than offset the cost of the meeting, turning in a net profit of \$5,655.00.

"Lastly, we are particularly gratified with the financial experience of the year. Our income for 1952 it is estimated will be \$382,000.00, whereas we only expected about \$335,000.00. The anticipated surplus for all operations and funds indicates a surplus of \$100,000.00, a net surplus for the General Fund of about \$69,000.00."

PRESIDENT MILLER: "I would like to support what Mr. Loveland has said about the exceedingly fine meeting which took place in Cuba, a multi-state Regional Meeting. Dr. Bortz also was in attendance. I would like to add also that an equally satisfactory multi-state Regional Meeting was held in Vancouver, B. C., which I attended a few weeks earlier."

DR. WALTER B. MARTIN: "I move the approval of the report, including the recommendation that we accept the 5% increase in the cost of the printing of the ANNALS, and that we go ahead with the Directory on the basis presented."

. . . The motion was duly seconded by Dr. A. B. Brower, put and carried. . . .

PRESIDENT MILLER: "May we have the report of the Committee on Membership, Dr. Richard A. Kern, Chairman?"

DR. KERN: "The Executive Office of the College through the past several months has completed a broad survey of medical school faculties, selected medical societies and Chiefs of Service of approved residencies in internal medicine, and the summary report is appended.

SUMMARY ANALYSIS OF A.C.P. MEMBERS AND NON-MEMBERS OF MEDICAL SCHOOL FACULTIES

Including only the Department of Medicine, and of following ranks:

Professor of Medicine
 Associate Professor of Medicine
 Clinical Professor of Medicine

Assistant Professor of Medicine
 Assistant Clinical Professor of Medicine
 Associate in Medicine

Medical School	ACP Associates	ACP Fellows	ACP Total	ACP %	Non-Mbrs.	Non-Mbr. %	Total Faculty	
Medical College of Alabama	8	16	24	70.6	10	29.4	34	
Univ. of Arkansas Sch. of Med.	5	18	23	30.8	37	60.2	60	
College of Medical Evangelists	7	19	26	52.0	24	48.0	50	
Univ. of Southern Calif. Sch. of Med.	12	33	45	51.7	42	48.3	87	
Stanford Univ. Sch. of Med.	4	18	22	44.9	27	55.1	49	
Univ. of California Sch. of Med.	5	23	28	45.9	33	54.1	61	
Univ. of Colorado Sch. of Med.	4	30	34	81.0	8	19.0	42	
Yale Univ. Sch. of Med.	5	15	20	40.8	29	59.2	49	
Georgetown Univ. Sch. of Med.	3	24	27	69.2	12	30.8	39	
George Washington Univ. Sch. of Med.	3	21	24	51.1	23	48.9	47	
Howard Univ. Coll. of Med.	2	3	5	55.6	4	44.4	9	
Medical College of Georgia	3	6	9	47.4	10	52.6	19	
Emory Univ. Sch. of Med.	4	12	16	59.3	11	40.7	27	
Chicago Medical School	2	6	8	21.6	29	78.4	37	
Northwestern Univ. Med. Sch.	4	51	55	69.6	24	30.4	79	
Univ. of Chicago Sch. of Med.	9	9	40.9	13	59.1	22		
Univ. of Illinois Coll. of Med.	15	49	64	56.6	49	43.4	113	
Indiana Univ. Sch. of Med.	10	22	32	62.7	18	37.3	50	
State Univ. of Iowa Coll. of Med.	6	7	13	76.4	4	23.6	17	
Univ. of Kansas Sch. of Med.	8	20	28	65.1	15	34.9	43	
Univ. of Louisville Sch. of Med.	8	26	34	81.0	8	19.0	42	
Louisiana State Univ. Sch. of Med	2	10	12	63.2	7	36.8	19	
Tulane Univ. Sch. of Med.	1	20	21	59.5	16	40.5	37	
Johns Hopkins Sch. of Med.	2	16	18	50.0	18	50.0	36	
Univ. of Maryland Sch. of Med.	4	22	26	53.1	23	46.9	49	
Boston Univ. Sch. of Med.	1	9	10	55.5	8	44.5	18	
Harvard Medical School		26	26	46.4	30	53.6	56	
Tufts College Medical School		10	10	33.3	20	66.7	30	
Univ. of Michigan Med. Sch.	4	11	15	65.2	9	34.8	24	
Wayne Univ. Coll. of Med.	4	18	22	66.7	11	33.3	33	
Univ. of Minnesota Med. Sch.	4	25	29	53.7	25	46.3	54	
St. Louis Univ. Sch. of Med.	3	14	17	68.0	8	32.0	25	
Washington Univ. Sch. of Med.	3	15	18	50.0	18	50.0	36	
Creighton Univ. Sch. of Med.		9	9	75.0	3	25.0	12	
Univ. of Nebraska Coll. of Med.	5	12	17	68.0	8	32.0	25	
State Univ. Med. Center at New York City		28	28	82.4	6	17.6	34	
Coll. of Med.		4	34	38	67.2	20	32.8	58
Univ. of Buffalo Sch. of Med.		4	43	47	53.4	41	46.6	88
Columbia Univ. Coll. of Phys. & Surgs.		6	25	31	43.1	41	56.9	72
Cornell Univ. Med. Coll.		18	55	73	44.0	92	56.0	165
New York Med. Coll., Flower & Fifth Avenue Hospitals		4	17	21	55.2	17	44.8	38
New York Univ. Coll. of Med.		2	7	9	33.3	18	66.7	27
Univ. of Rochester Sch. of Med.		7	13	20	80.0	5	20.0	25
Duke Univ. Sch. of Med.		2	8	10	76.9	3	23.1	13
Bowman Gray Sch. of Med. of Wake Forest College		7	22	29	80.6	7	19.4	36
Univ. of Cincinnati Coll. of Med.			13	13	42.0	18	58.0	31
Western Reserve Univ. Sch. of Med.	205	910	1,115		902		2,017	

SUMMARY ANALYSIS OF A.C.P. MEMBERS AND NON-MEMBERS—Continued

Medical School	ACP Associates	ACP Fellows	ACP Total	ACP %	Non-Mbrs.	Non-Mbr. %	Total Faculty
Brought Forward	205	910	1,115		902		2,017
Ohio State Univ. Coll. of Med.	8	16	24	60.0	16	40.0	40
Univ. of Oklahoma Sch. of Med.	1	19	20	66.6	10	33.4	30
Univ. of Oregon Med. Sch.	6	26	32	65.3	17	34.7	49
Hahnemann Med. Coll. & Hosp. of Phila.	3	7	10	35.7	18	64.3	28
Jefferson Med. Coll. of Phila.	5	21	26	59.1	18	40.9	44
Temple Univ. Sch. of Med.	1	14	15	65.2	8	34.8	23
Univ. of Pennsylvania Sch. of Med.	7	41	48	66.6	24	33.4	72
Woman's Med. Coll. of Pennsylvania	2	8	10	71.5	4	28.5	14
Univ. of Pittsburgh Sch. of Med.	5	21	26	45.6	31	54.4	57
Med. Coll. of the State of South Carolina	2	5	7	58.4	5	41.6	12
Univ. of Tennessee Coll. of Med.	1	15	16	80.0	4	20.0	20
Meharry Medical College	3	2	5	31.3	11	68.7	16
Vanderbilt Univ. Sch. of Med.	1	16	17	70.9	7	29.1	24
Southwestern Med. Sch. of Univ. of Texas	1	27	28	66.7	14	33.3	42
Univ. of Texas Medical Branch	1	9	10	100.0			10
Baylor Univ. Coll. of Med.	9	32	41	63.0	24	37.0	65
Univ. of Utah Coll. of Med.	1	9	10	40.0	15	60.0	25
Univ. of Vermont Coll. of Med.	4	4	8	72.8	3	27.2	11
Univ. of Virginia Dept. of Med.		6	6	60.0	4	40.0	10
Univ. of Washington Sch. of Med.	1	22	23	41.8	32	58.2	55
Univ. of Wisconsin Med. Sch.	1	9	10	58.8	7	41.2	17
Marquette Univ. Sch. of Med.	6	33	39	73.6	14	26.4	53
	274	1,272	1,546	56.5	1,188	43.5	2,734

No 1952 Catalogs Published as Yet:
 Stritch Sch. of Med. of Loyola Univ.
 Albany Medical College
 State Univ. of New York Coll. of Med. at Syracuse
 Medical College of Virginia

Medical School (Canadian)	ACP Associates	ACP Fellows	ACP Total	ACP %	Non-Mbrs.	Non-Mbr. %	Total Faculty
Univ. of Alberta Fac. of Med.	1	4	5	83.3	1	16.7	6
Univ. of Manitoba Fac. of Med.	1	7	8	53.3	7	46.7	15
Dalhousie Univ. Fac. of Med.		3	3	30.0	7	70.0	10
Queen's Univ. Fac. of Med.	3	9	12	63.2	7	36.8	19
Univ. of Western Ontario Fac. of Med.		5	5	45.5	6	54.5	11
Univ. of Toronto Fac. of Med.	1	8	9	30.0	21	70.0	30
McGill Univ. Fac. of Med.	2	16	18	64.3	10	35.7	28
*Univ. of Montreal Fac. of Med.							
Laval Univ. Fac. of Med.							
	8	52	60	50.4	59	49.6	119

* No figures.

The Committee reviewed the results of the survey into the medical school faculties and the percentage of faculty members who are members of the College; also a review of the membership of certain selected medical societies and also of the Chiefs of Service of approved residencies in internal medicine.

From the standpoint of the faculties of the medical schools—and here only those listed in the faculty of internal medicine in those schools were checked, ranging from Associates up to Professors—all but four of the schools in the United States and

Canada were checked. Those that were not checked did not have catalogs available at the time.

"It turns out that 56.5% of the members of medical school faculties in the United States and 50.4% of those in Canada are members of the College. In the two-year basic science schools only 24.4% of the faculties are members of the College. However, the significance of these figures depends primarily on the numbers involved, so that the total members of medical school faculties in the United States in the four-year schools was 2,734, of whom 1,546 are College members and 1,188 are non-members. In Canada the figures are a total 119, of whom 60 are College members and 59 non-members. This is for the four-year schools.

"The total number involved in the two-year schools is very small. There are only 41 members of medical faculties, 10 of whom are in the College and 31 are not.

"In making this survey an exact listing of faculty members of all the medical schools was made, together with a notation of their academic rank and whether they are or are not Fellows or Associates of the College. As one looks over this list, he is impressed with the great variability not on a regional basis, but locally in the same city. For example, the lowest percentage of a four-year school, as far as membership in the College is concerned, is the Chicago Medical School, 21.6%; yet in the same city, Northwestern University has practically 70% of its faculty as members of the College. In the Chicago Medical School 2 of 4 Professors are not members of the College and 7 of 9 Associate Professors are not members of the College; 10 of 13 Assistant Professors are not members and 10 of 11 Associates are not members. One could cite similar figures for Philadelphia, where the range is between a low 35.7% for Hahnemann Medical College and a high of 71.5% for the Woman's Medical College.

"The check of certain individual schools is at times surprising too. For example, at Harvard 53.6% are not members of the College—that in spite of the fact that there are on the faculty such men as Bauer, Blumgart, Joslin and Levine who are College Fellows; the University of Rochester, where Dr. William S. McCann is very active, still has 66.7% not in the College; Cornell, under Dr. David P. Barr, has 53% outside the College; Johns Hopkins, 50-50.

"From the standpoint of selected societies five were checked, American Clinical and Climatological Association, American Gastro-enterological Association, American Society for Clinical Investigation, Association of American Physicians and the Central Society for Clinical Research. The best record is that of the American Clinical and Climatological Association, where 81% of its members are in the College and those who are not happen to have other interests, such as dermatology, pediatrics, psychiatry and a few others. The American Gastro-enterological Association has 66% in the College, but there are many members of that society who are surgeons and not interested in the College. The American Society for Clinical Investigation has only 40% in the College, but that is a much younger age group, and, consequently, has fewer members. I believe also it has a certain number of members who are non-physicians, or those without clinical interest. The Association of American Physicians has 60.4% who are members of the College, and the Central Society for Clinical Research has 59.5% membership from the College.

"From the standpoint of Chiefs of Service of hospitals where there are approved residency training programs in internal medicine there are 604 such Chiefs, 427 of whom, or 70%, are in the College; only 177 are not in the College, and in part at least these are in an older age group who are not interested. It is significant, although the total numbers involved are small, that the Chiefs of Service in the federal hospitals show the best record—77% of their Chiefs of Service being College members.

"Your Committee feels that it would be desirable to find out some of the reasons why there are approximately 1,200 members of medical faculties in the United States

SURVEY OF APPROVED RESIDENCIES AND FELLOWSHIPS IN INTERNAL MEDICINE, WITH REGARD TO CHIEFS OF SERVICE IN CHARGE THEREOF

	ACP Associates	ACP Fellows	ACP Total	ACP %	Non- Mbrs.	Non- Mbr. %	Total Chiefs
Part I:							
Federal Hospitals:							
U. S. Army	2	5	7	100.	0	00.	7
U. S. Navy		6	6	75.	2	25.	8
U.S.P.H.S.	2	2	4	50.	4	50.	8
Federal Security Agency							
Veterans Admn.	9	1	1	100.	0	00.	1
	—	30	39	78.	11	22.	50
	13	44	57	77.	17	23.	74
Part II:							
Non-Federal Hospitals	30	340	370	70.	160	30.	530
Summary:							
Federal Hospitals	13	44	57	77.	17	23.	74
Non-Federal Hospitals	30	340	370	70.	160	30.	530
	43	384	427	70.7	177	29.3	604

and Canada who are not members of the College, to find the reasons why they are not members. Then as a fact-finding measure—and we underline that it is not a proselytizing procedure—it is recommended that a letter be sent to the Governors, asking them their assistance in finding out why non-members comprise the percentage that they do of certain faculties in their area; that the Governors be asked to look into and advise as to whom one might direct an inquiry with regard to these several schools. This might be done by selecting a key man in a given school who is interested in the College and who could best answer for his own school; or in the case of several schools in a city, one with an excellent record and another not so good, the inquiry might be directed to a faculty member of the school with a better representation to make discreet inquiry as to why the other school wasn't doing as well as it might; and in the case where a school might be the only one in a city that a suitable person be approached in that area or in the Governor's general district.

"It is the feeling of the Committee that non-membership must be due to a variety of possibilities. Obviously, some are not qualified. It is, however, quite likely that some were overlooked, individuals who are diffident about applying, who expect to be approached rather than themselves to seek to gain membership. Then it might also be true that in some instances an injustice occurred or a mistake was made that kept some good men out.

"From the standpoint of the five societies that were surveyed, obviously, nothing in the way of action is called for. That part of the report is purely informative, nor is there any direct approach considered at this time to the matter of the Chiefs of Service—that might readily be the subject of some further study."

Dr. WALLACE M. YATER: "I move the recommendations be adopted."

. . . The motion was seconded by Dr. Edward L. Bortz, put and carried. . . .

Dr. George Morris Piersol, Chairman of the Committee on Credentials, presented the report of that Committee concerning membership problems in Western Canada and Hawaii, elections to Associateship and Fellowship and other relevant matters. Action growing out of the report of this Committee resulted in the following:

- (1) An Associate was dropped because of failure to take up election within the period specified by the By-Laws.

(2) The following Associates were reinstated for periods as indicated (all of these cases fall within the amendment to the By-Laws adopted at the Annual Business Meeting of April 24, 1952) :

William Wolf Abrams, Kansas City, Kans. (to November, 1957)
Arnold V. Arms, Kansas City, Mo. (to April, 1958)
Phyllis J. Burdon, Topeka, Kans. (to November, 1957)
Thomas Edison Clark, Columbus, Ohio (to November, 1957)
Jack Quillian Cleveland, Coral Gables, Fla. (to November, 1957)
Forest Hilton Coulson, Burlington, Iowa (to November, 1957)
John Lawson Elliott, Savannah, Ga. (to November, 1957)
Matthew James Mackinnon Ellis, Mountain Home, Tenn. (to November, 1957)
George Bache Emory, Jr., Morristown, N. J. (to November, 1957)
John Otto Gibbs, San Francisco, Calif. (to November, 1957)
Clifford H. Hansen, Omaha, Nebr. (to November, 1957)
Frederic A. Kramer, Sr., St. Louis, Mo. (to November, 1957)
Jack Damgaard Lange, Los Altos, Calif. (to November, 1957)
Monroe Franklin Loy, San Marino, Calif. (to November, 1957)
Porter Kahn Mason, Dallas, Tex. (to November, 1957)
Oscar Clarence McCarn, Birmingham, Ala. (to November, 1957)
Harold Edmund Miller, Minneapolis, Minn. (to November, 1957)
John Edward Moss, Mobile, Ala. (to April, 1958)
S. Edwin Muller, Baltimore, Md. (to November, 1957)
Everett William Probst, Arlington, N. J. (to November, 1957)
James Paul Proudit, Washington, Pa. (to November, 1957)
Joseph Handley Rogers, Gadsden, Ala. (to November, 1957)
George Parke Rouse, Jr., Philadelphia, Pa. (to November, 1957)
Joseph Frank Sandella, New Brunswick, N. J. (to April, 1958)
John Kenneth Thompson, Fort Smith, Ark. (to November, 1957)
David Highbaugh Thurman, Louisville, Ky. (to November, 1957)
Frank Walter Van Kirk, Jr., Los Angeles, Calif. (to November, 1957)
Vernon Van Zandt, Los Angeles, Calif. (to November, 1957)
Louis Gordon Welt, Chapel Hill, N. C. (to November, 1957)
Walter Kellogg Whitehead, Detroit, Mich. (to November, 1957)
Horace Helmut Zinneman, Minneapolis, Minn. (to November, 1957)

(3) Five applications for reinstatement were disapproved and three applications for reinstatement were deferred.
(4) 266 candidates were elected to Associateship and 89 candidates were elected to Fellowship (lists of names have been published previously in these columns).
(5) The Committee on Credentials was requested particularly to review the case of a candidate who, though having outstanding qualifications, had permanently removed from his original Province to a permanent location in the United States after his proposal was submitted. Under regulations of the Board of Regents and the By-Laws, a candidate must be established for a period of two to three years in a permanent location prior to election to the College.

Dr. Moffatt inquired about the status of Canadian applications for membership in the College. Secretary Loveland reviewed the matter by saying that for many years the Committee on Credentials and the Board of Regents have followed the principle that candidates for membership shall be citizens of a North American Country. In the case of other countries than the United States and Canada, there has been the further recommendation that such candidates shall be able to read and speak English. Membership in the College is an active matter. A man should not seek Fellowship just for the honor of it, but he should benefit from his association

with the College and be able also to make contributions. If he is going to be in North America but for a temporary time, or if he is unable to comprehend English, it is obvious that he cannot receive or gain any benefit through Fellowship. There are men who are studying in this country from many other lands—men who are not going to stay, but who would like to have the honor of a "F.A.C.P." Such individuals have been advised, when they have sent inquiries to the College, that they are not eligible for membership.

Dr. Yater expressed the opinion that candidates should either be citizens or should have applied for citizenship.

Dr. Lewis inquired whether it would be of value to poll the Governors and Regents of the College in Canada to determine what their feeling is on the subject.

Dr. Moffatt, of Montreal, pointed out that there is only one Province in Canada which exacts Canadian citizenship before full licensure, and it requires five years to become a Canadian citizen. Some of the candidates now being proposed for Associateship are not yet legally Canadians. They may be Englishmen who are coming to Canada. Dr. Moffatt further stated that he had obtained letters from two Canadian Governors who think non-citizenship should not be a barrier. He felt that if the matter were left in the same way it has been for the past few years, the Canadian Governors and Regents will be quite satisfied. He pointed out that membership in the Canadian Medical Association does not require citizenship, but does specify certain other qualifications. He thought that ultimately it will come about that Canada will exact the legal citizenship requirement.

The President then called for the report of the Treasurer:

DR. WILLIAM D. STROUD: "The Treasurer's Report is supplementary to that of the Committee on Finance. That Committee will report on the investment of surplus funds, any changes recommended for the present portfolio and related subjects. The present security holdings of the College are as follows:

	<i>Book Value</i>	<i>Market Value</i>	<i>Appreciation</i>
Endowment and Trust Funds	\$407,162.29	\$432,842.00	\$ 25,679.71
General Fund	362,257.04	451,411.00	89,153.96
	<hr/>	<hr/>	<hr/>
	\$769,419.33	\$884,253.00	\$114,833.67

"The annual cash income from securities on our present holding basis is estimated by our investment counselor as \$41,673.00, with an average yield of 4.71%. This compares with 4.53% for 1951 and 4.58% for 1950.

"Close contact is maintained with our investment counselors, Drexel & Co., we obtain regular analyses of our accounts from them, and we have their representatives meet with us at the autumn meeting of the Committee on Finance each year."

. . . On motion by Dr. A. B. Brower, seconded by Dr. Herbert K. Detweiler, put and carried, the report of the Treasurer was accepted. . . .

PRESIDENT MILLER: "Will Dr. Stroud proceed with a report for the House Committee?"

DR. STROUD: "During 1952 we have had a combination of repairs and replacements that have developed more or less in a single year, which have not occurred in any other single year and which probably will not occur again in a single year.

"For instance, the copper gutters on the older section of the Building had to be replaced at a cost of \$1,800.00, this being the first time they had been replaced since the building was constructed in 1906. It is, therefore, unlikely that this expense will be incurred in the next twenty years. Another item was painting the Building, \$735.00; installation of new private offices for the Bookkeeping Department and for one of the Executive Assistants, \$1,680.00; pointing and caulking the building, \$851.34, and ordinary maintenance, \$685.30. This work was all authorized by the Regents

a year ago. The Building is now all in good condition and no exceptional maintenance expenses are anticipated in the coming year.

"The House Committee also reports on the property next door, 404-12 S. 42nd Street, which is occupied by a tenant at a rental of \$1,800.00 per annum. We do not find the current tenant fully satisfactory, in view of the fact that he fails to maintain the grounds during the summer period in acceptable condition, and we anticipate the termination of his lease on June 1, 1953, when a new tenant will be sought. The rate of income on the investment in the purchase of that property for 1952 will be just under 6%."

. . . On motion by Dr. Walter B. Martin, seconded by Dr. Walter L. Palmer, put and carried, this report was accepted. . . .

PRESIDENT MILLER: "May we now have the report of the Committee on Fellowships and Awards, Dr. Cyrus C. Sturgis, Chairman?"

DR. CYRUS C. STURGIS: "The Committee on Fellowships and Awards met at the College Headquarters on November 14-15, 1952, with the following in attendance: Dr. Cyrus C. Sturgis, Chairman, and Dr. Wallace M. Yater, and with Dr. M. R. Kinde, Director, Division of Medicine and Public Health, W. K. Kellogg Foundation, Dr. E. Hugh Luckey, Director of the Orientation Course at Cornell University, and Mr. E. R. Loveland, Executive Secretary. Dr. Charles A. Doan, Dr. William C. Menninger and Dr. Wesley W. Spink were absent.

"The report of the Committee includes two meetings since the last meeting in Cleveland—the first meeting at Ann Arbor, Mich., on June 21, 1952, and the second meeting at the College Headquarters on November 14-15, 1952.

June 21, 1952, Meeting at Ann Arbor:

"This meeting was attended by Dr. Cyrus C. Sturgis, Chairman, Dr. Douglas Donald (substituting for Dr. Charles A. Doan), Dr. William C. Menninger, Dr. Wesley W. Spink, Dr. Wallace M. Yater, Dr. T. Grier Miller, President, Mr. E. R. Loveland, Executive Secretary, Dr. Benjamin G. Horning, Kellogg Foundation, Dr. M. R. Kinde, Kellogg Foundation, and Dr. E. Hugh Luckey, Cornell University.

"Minutes of the last meeting of the Committee at Cleveland, April 22, 1952, were approved as read.

"Chairman Sturgis gave some details about the program of Dr. Daniel Harvey Labby, one of the two 1952 A. Blaine Brower Traveling Scholars, and then gave a full review of the program carried out by Dr. William H. Bates, of Cottonwood, Ariz., the other Brower Scholar for 1952.

"The Executive Secretary then advised the Committee that Dr. James Edwin Wood, III, to whom a Research Fellowship had been awarded for 1951-52, but who could not accept it because of military duty, had informed the College of the acceptance of a permanent appointment and will not in the future be interested in pursuing this fellowship. Thus the funds, \$3,500.00, previously held in reserve for him, have been turned back to the Research Fellowship Reserve Fund.

"A letter was reviewed by Dr. Reginald Fitz, in which he expressed the opinion that the College may be losing some of the best Research Fellow applicants because it requires their applications be filed by October 1. The Committee discussed the matter at length, and held to the opinion that applications must be received in time for processing and action at the November meeting of the Board of Regents, and expressed the belief that the closing date, October 1, is not too early, nor does it interfere with obtaining good candidates. The Committee reviewed at some length the matter of increased publicity concerning the College Research Fellowships. Presently the notices are sent to the Deans of Medical Schools, Professors of Medicine, Professors of Pediatrics and a selected list of names furnished by the Chairman of the Committee. The Executive Secretary was asked to consider the possibility of

sending an appropriate notice, perhaps an enlarged card, to the Medical Directors or Superintendents of Hospitals approved for residencies in Medicine, and it was agreed that this shall be done (it was done and we had 27 applicants for this year, which is a considerable increase over previous years).

"Applications for extension of Latin-American Fellowships were submitted for the following:

Dr. Aloysio de Salles FONSECA, Rio de Janeiro, Brazil, S. A.

Dr. Jose Antonio GARCIA Reyes, Mexico, D. F.

Dr. Roberto Figueira SANTOS, Salvador, Brazil, S. A.

and the extensions were approved by the Kellogg Foundation and the Committee.

"The Committee then reviewed the ten (10) Latin-American Fellows selected in 1950, receiving the final reports from the Preceptors in those cases for which final reports had not previously been received; the concluding dates of each fellowship and the status of the issuance of their certificates were recorded.

"The Committee then reviewed the programs of ten (10) Latin-American Fellows who started in 1951. Interim reports were presented from the Preceptors and satisfactory progress was noted in every case.

"New applications for Latin-American Fellowships were then presented for review, and the following approved:

1. Dr. Nicolas Enrique BREUER, Asuncion, Paraguay, S. A.
2. Dr. Luis Alberto CACERES Carisimo, Asuncion, Paraguay, S. A.
3. Dr. Fabio CASTILLO Figueroa, San Salvador, El Salvador, C. A.
4. Dr. Hugo DONOSO Puelma, Santiago, Chile, S. A.
5. Dr. Jorge ESPINO Vela, Mexico, D. F.
6. Dr. Jose Esteban GRASSI Ricagni, Asuncion, Paraguay, S. A.
7. Dr. Carlos GUZMAN Lira, Santiago, Chile, S. A.
8. Dr. Magid IUNES, Mexico, D. F.
9. Dr. Guido MIRANDA Gutierrez, San Jose, C. A.
10. Dr. Eustaquio Dario MONTERO, Montevideo, Uruguay, S. A.
11. Dr. Abel OLMO Calcagni, Concepcion, Chile, S. A.
12. Dr. Oscar PERALTA Vallejos, Santiago, Chile, S. A.
13. Dr. Jose M. PORTILLA, Quito, Ecuador, S. A.
14. Dr. Helio PUCCI, Sao Paulo, Brazil, S. A.
15. Dr. Carlos Maria RAMIREZ Boettner, Asuncion, Paraguay, S. A.
16. Dr. Oscar ROBLEDO Restrepo, Medellin, Antioquia, Colombia, S. A.
17. Dr. Alvaro TORO Mejia, Medellin, Antioquia, Colombia, S. A.
18. Dr. Leopoldo A. VASQUEZ, Santiago, Chile, S. A.

"There followed a discussion re Latin-American Fellowship regulations, and the Committee modified the paragraph concerning the College officially sending out notifications, omitting announcements from the College to the 'local Selection Committee,' notification going only to the candidate direct; the paragraph providing for all Latin-American Fellows to first proceed to the office of the American College of Physicians for instructions shall be deleted, since the interview with the Committee in the midst of their Orientation Course shall be substituted. It was further agreed that the College shall in the future deliver the Certificates through the United States Ambassador for the candidate's country, the Kellogg Foundation to furnish the Executive Office of the College with the name and address of the appropriate Ambassador.

"The Chairman then distributed a list of nominations that had been received from Regents and Governors of the College and from Professors of Medicine for the James D. Bruce Memorial Award for 1953. After general discussion of the list, it was so moved that Dr. Thomas Francis, Ann Arbor, Mich., be recommended to the

Executive Committee of the Board of Regents as the Bruce Memorial Medalist for 1953; this motion was seconded and unanimously carried.

"Chairman Sturgis then distributed a list of nominations for the John Phillips Memorial Award for 1953 that had been received from the same source as the Bruce Award, and it was moved, seconded and unanimously carried that the nomination of Dr. Charles H. Best, Toronto, Ont., Canada, be recommended to the Executive Committee of the Board of Regents as the John Phillips Memorial Medalist for 1953.

"Subsequently, both nominations were submitted to the Executive Committee of the Board of Regents and were unanimously approved.

"It was suggested that if Dr. Thomas Francis is the recipient, that his report and lecture be on the subject of influenza, rather than poliomyelitis, because the 1952 recipient, Dr. James H. S. Gear, spoke on the latter subject.

"The Committee approved the revised announcement sent to all Associates of the College concerning the two 1953 Brower Traveling Scholarships, the revision pointing out that those who have applied previously, but who failed to receive an award, are not excluded from reapplying for the coming year.

"The Committee reopened a discussion of the amount of the stipend offered for Research Fellowships by the College, namely, \$3,000.00 to unmarried recipients; \$3,500.00 to married recipients; \$3,500.00 to an unmarried Research Fellow designated as the 'Alfred Stengel Research Fellow'; and \$4,000.00 to a married 'Alfred Stengel Research Fellow.' The Executive Secretary presented an outline of the stipends of comparable fellowships by other organizations, and the Committee decided not to recommend a change in the present fellowship stipends of the College, believing that eventually, after the military situation has improved, an adequate number of candidates will be received.

"This concludes the report of the meeting in Ann Arbor.

November 14, 1952, Meeting at Philadelphia:

"The meeting opened with a luncheon at the Penn Sheraton Hotel at 12:00 M., with Dr. Cyrus C. Sturgis, Chairman, Dr. Wallace M. Yater, of the Committee, Dr. M. R. Kinde, of the Kellogg Foundation, Dr. E. Hugh Luckey, Director of the Orientation Course at Cornell, Dr. T. Grier Miller, President of the College, and Mr. E. R. Loveland, Executive Secretary, in attendance, as well as the eleven (11) current Latin-American Fellows presently pursuing the Orientation Course at Cornell. After the luncheon appropriate remarks were made by Chairman Sturgis, President Miller, Mr. Loveland, Dr. Kinde, Dr. Yater and Dr. Luckey, after which the eleven Latin-American Fellows were individually interviewed, as follows:

1. *Dr. Nicolas Enrique BREUER, Asuncion, Paraguay, S. A.*

Specialty, Endocrinology, Neurology and General Medicine; presently enrolled in the Orientation Course at Cornell University; on March 1, 1953, he will report to the University of Michigan, under the Preceptorship of Dr. Cyrus C. Sturgis for a period of one year.

2. *Dr. Luis Alberto CACERES Carisimo, Asuncion, Paraguay, S. A.*

Specialty, Pediatrics; presently enrolled in the Orientation Course at Cornell University; Dr. Cyrus C. Sturgis to contact Dr. Irvine McQuarrie, Professor of Pediatrics at the University of Minnesota Medical School, to determine if Dr. Caceres may work with him for one year in the field of Pediatrics, beginning March 1, 1953.

3. *Dr. Fabio CASTILLO Figueroa, San Salvador, El Salvador, C. A.*

Specialty, Physiology and Internal Medicine; presently enrolled in the Orientation Course at Cornell University; upon return to his home country will be Professor of Physiology; Mr. E. R. Loveland to contact Dr. Julius H. Comroe, Jr., Professor of

Physiology and Pharmacology, University of Pennsylvania Graduate School of Medicine, to determine if Dr. Castillo may work with him in his department for one year, beginning March 1, 1953, and also to determine if Dr. Castillo may obtain through Dr. Paul Gyorgy some training in biochemistry.

4. *Dr. Hugo DONOSO Puelma, Santiago, Chile, S. A.*

Specialty, Pulmonary Disease; presently enrolled in the Orientation Course at Cornell University; originally assigned to the Orientation Course for three months, but extension requested for an additional three months in the Orientation Course. This is agreeable to his sponsors and to the Kellogg Foundation, and Dr. Donoso will remain in the Orientation Course to March 1, 1953. Is interested in a year in broad Internal Medicine, but with special work in pathologic physiology and pulmonary disease. Dr. Cyrus C. Sturgis to contact Dr. A. McGehee Harvey, Johns Hopkins University School of Medicine, to determine if Dr. Donoso may work with him for one year, beginning March 1, 1953. Dr. E. Hugh Luckey, Director of the Orientation Course, advises that this is an outstanding man.

5. *Dr. Magid IUNES, Mexico, D. F.*

Specialty, Biological Chemistry and Metabolic Diseases; presently enrolled in Orientation Course at Cornell University; originally assigned to report directly to Dr. Ancel Keys of the University of Minnesota, but due to Dr. Keys' absence from the country, enrolled in the Orientation Course for six months. Mr. E. R. Loveland to contact Dr. Wesley W. Spink to determine if arrangements can be made for Dr. Iunes to work with Dr. Keys for one year, beginning March 1, 1953.

6. *Dr. Guido MIRANDA Gutierrez, San Jose, C. R.*

Specialty, Cardiology; presently enrolled in Orientation Course at Cornell University; Dr. Miranda interested in General Internal Medicine training as an observer. Dr. Cyrus C. Sturgis to contact Dr. William S. McCann, Dewey Professor of Medicine, University of Rochester School of Medicine, to determine if Dr. Miranda may work with him for one year, beginning March 1, 1953.

7. *Dr. Abel OLmos Calcagni, Concepcion, Chile, S. A.*

Specialty, Internal Medicine, Gastro-enterology; will work with Dr. Biel, a former Latin-American Fellow, at Concepcion University upon his return home. Dr. Cyrus C. Sturgis to contact Dr. Walter L. Palmer, University of Chicago School of Medicine, to determine if Dr. Olmos may work with him for a period of one year, beginning March 1, 1953; if Dr. Palmer is unable to take him on, then Dr. Sturgis to contact Dr. Sara M. Jordan, Lahey Clinic, Boston, Mass. Dr. Olmos is presently enrolled in the Orientation Course.

8. *Dr. Oscar PERALTA Vallejos, Santiago, Chile, S. A.*

Specialty, Gastro-enterology; upon his return to his home country will be in charge of Gastroenterology Department. Originally assigned to the Orientation Course for three months, but Orientation Course now extended to six months, to March 1, 1953, with approval of his sponsors and the Kellogg Foundation. Arrangements have been completed for Dr. Peralta to work with Dr. Thomas E. Machella, University of Pennsylvania School of Medicine, Philadelphia, for one year, beginning December 1, 1952, but Mr. E. R. Loveland to contact Dr. Machella to determine if it will be satisfactory for him to take Dr. Peralta on for one year, beginning March 1, 1953.

9. *Dr. Jose M. PORTILLA, Quito, Ecuador, S. A.*

Specialty, Clinical Nutrition; presently enrolled in the Orientation Course at Cornell University; Dr. Portilla must return to his home country at the end of August, 1953. Dr. Cyrus C. Sturgis to contact Dr. Grace Goldsmith at Tulane Uni-

versity of Louisiana School of Medicine, New Orleans, to determine if Dr. Portilla may work with her from January 1, 1953, through June 30, 1953; Dr. M. R. Kinde to make arrangements for Dr. Portilla to spend the months of July and August, 1953, in Guatemala.

10. *Dr. Helio PUCCI, Sao Paulo, Brazil, S. A.*

Specialty, Gastro-enterology; presently enrolled in Orientation Course at Cornell University. Dr. E. Hugh Luckey to contact Dr. Thomas Almy, Cornell University Medical College, New York, N. Y., to determine if Dr. Pucci may work with him for a period of one year, beginning March 1, 1953; Dr. Luckey to inform Dr. Sturgis whether or not Dr. Almy will accept the Preceptorship; if not, Dr. Cyrus C. Sturgis to contact Dr. Chester M. Jones.

11. *Dr. Leopoldo A. VASQUEZ, Santiago, Chile, S. A.*

Specialty, Internal Medicine and Medical Teaching; presently enrolled in Orientation Course at Cornell University. Dr. Vasquez would like special work in cardiology and would also like to observe teaching methods. Dr. Cyrus C. Sturgis to contact Dr. Chester S. Keefer, Wade Professor of Medicine, Boston University School of Medicine, to determine if Dr. Vasquez may work with him for a period of one year, beginning March 1, 1953. If Dr. Keefer is unable to accept Dr. Vasquez, Dr. Sturgis to contact Dr. W. Barry Wood, Professor of Medicine, Washington University School of Medicine, St. Louis, Mo.

"Also interviewed at this meeting was Dr. Carlos Maria RAMIREZ Boettner, Asuncion, Paraguay, S. A., presently assigned to Dr. Cyrus C. Sturgis, University Hospital, Ann Arbor, Mich., for six months, September 1, 1952, through February 28, 1953, and then possibly balance of time at Cornell University under Dr. David P. Barr, New York, N. Y., for six months. Dr. Ramirez still would like to go to Cornell under Dr. Barr; Dr. Kinde approved this arrangement, and Dr. Cyrus C. Sturgis to contact Dr. David P. Barr to determine if he will take Dr. Ramirez under his Preceptorship for a period of six months, beginning March 1, 1953.

"The Committee also reviewed the cases of the seven Latin-American Fellows previously approved at the June, 1952, meeting of the Committee, but who were not interviewed at this meeting, inasmuch as in three instances their programs have been delayed, and in four cases their programs have already been established. However, in the case of Dr. Eustaquio Dario MONTERO, Montevideo, Uruguay, S. A., who is presently enrolled in the University of Pennsylvania Graduate School of Medicine, in the formal course in Dermatology and Syphilology, as assigned to Dr. Ains C. McGuinness, who requested an additional year, Mr. E. R. Loveland is to get an evaluation report from Dr. McGuinness. If his record is good and he has promise, it is agreeable to the Kellogg Foundation and the Committee to give him another year, probably a residency; Mr. Loveland to inform Dr. Kinde of the report from Dr. McGuinness.

"The following four (4) Latin-American Fellows have completed their work and returned home, and their Certificates have been issued to them:

1. *Dr. Carlos HEINRICH Treuer, Concepcion, Chile, S. A.*

Terminated his fellowship on August 4, 1952 (prior to December 1, 1952); report from Dr. Gordon B. Myers already made to Committee; Certificate signed by Dr. Gordon B. Myers, Preceptor; issued under date of August 4, 1952, for period September 4, 1951, to August 4, 1952.

2. *Dr. Ruy PEREZ TAMAYO, Mexico, D. F.*

Final reports from Preceptors filed; Certificate signed by Dr. Robert A. Moore, Preceptor; issued under date of September 25, 1952, for period September 20, 1950, to September 20, 1952.

3. Dr. Valdir Cordeiro PESSOA, Recife, Pernambuco, Brasil, S. A.

Preceptor's final report filed; Certificate signed by Dr. A. C. Ivy, Preceptor; issued under date of September 20, 1952, for period September 13, 1950, to February 22, 1951, and September 8, 1951, to September 15, 1952 (showing the interruption of his fellowship due to the illness of his father and his return to Brazil).

4. Dr. Francisco RIVADENEYRA Hinojosa, Morelia, Mexico

Due to the fact he had only one year of leave with the Army, his assignment at the Lahey Clinic ended after a period of six months. Preceptor's final report filed. Certificate signed by Dr. Sara M. Jordan, Preceptor; issued under date of September 15, 1952, for period September 4, 1951, to August 23, 1952.

"The following Latin-American Fellows are still working in the institutions to which they were previously assigned by the Committee, and satisfactory interim reports have been received concerning their activities:

1. Dr. Jorge ARAUJO Grau, Bogota, Colombia, S. A.

Specialty, Internal Medicine; working under Preceptorship of Dr. E. Hugh Luckey and Dr. David P. Barr, New York Hospital, since December 1, 1951 (to November 30, 1952). Dr. Araujo applied to the Kellogg Foundation for an extension of seven months, to June 30, 1953, and it was moved, seconded and approved, both by the Committee and the Kellogg Foundation.

2. Dr. Jose BARZELATTO Sanchez, Santiago, Chile, S. A.

Specialty, Internal Medicine; Preceptorship of Dr. Walter Bauer, Massachusetts General Hospital, December 1, 1951, through November 30, 1952; candidate working chiefly under Dr. John B. Stanbury; fellowship extended three months, through February 28, 1953, by Kellogg Foundation, enabling him to spend the month of December, 1952, with Dr. Rulon Rawson at the Memorial Hospital, New York City, and the months of January and February, 1953, at the Oak Ridge Institute of Nuclear Studies; final report filed by Dr. Stanbury; work will be concluded February 28, 1953.

3. Dr. Adolfo BISSO Zollner, Lima, Peru, S. A.

Specialty, Endocrinology; fellowship under Preceptorship of Dr. Francis C. Wood, University of Pennsylvania, and specifically assigned to Dr. Edward Rose, 3-1-52 to 2-28-53.

4. Dr. Jose CARA, Cordoba, Argentina, S. A.

Specialty, Internal Medicine; working under Preceptorship of Dr. Lawson Wilkins, Johns Hopkins Hospital, Baltimore, 3-1-52 to 2-28-53.

5. Dr. Alvaro CARBALLO Montero, San Jose, Costa Rica, C. A.

Specialty, Gastro-enterology; fellowship under Preceptorship of Dr. H. Marvin Pollard, University of Michigan, 3-1-52 to 2-28-53. Dr. Carballo applied through Kellogg Foundation for an extension of his fellowship and would like to start training in Surgery, January 1, 1953. Dr. Cyrus C. Sturgis to contact Dr. Lahey to determine if he will take on Dr. Carballo for six months, March 1, 1953, through August 31, 1953, who desires to observe American surgical methods, etc.; fellowship, therefore, extended for six months.

6. Dr. Jose Antonio GARCIA Reyes, Mexico, D. F.

Specialty, Internal Medicine; under Preceptorship of Dr. George W. Thorn for six months; granted an extension to 10-31-52, working under Dr. Peter H. Forsham, University of California since 6-1-52; further extension granted for six months, from 11-1-52 through 4-30-53, to work on a research problem under Dr. Forsham, when work will be concluded.

7. Dr. Otto HERRMANN Koch, Santiago, Chile, S. A.

Specialty, Vascular Diseases; working under Preceptorship of Dr. Irving S. Wright, New York Hospital, 3-1-52 to 2-28-53. At the end of fellowship would like one week at the Mayo Clinic; Dr. Wright to contact Dr. Edgar V. Allen.

8. Dr. Arturo PINEDA Giraldo, Medellin, Colombia, S. A.

Specialty, Internal Medicine; under Preceptorship of Dr. Walter L. Palmer, University of Chicago, 3-1-52 to 2-28-53, when work will be concluded.

"This concludes our report so far as the Latin-American Fellows are concerned.

"*A.C.P. Research Fellowships*—The Committee reports that three of the six 1951-52 Research Fellows concluded their work, and that the Committee received from each candidate a detailed report on the work accomplished and manuscripts or publications emanating therefrom. Certificates have been issued to them, signed by the proper Officers of the College and their Preceptors. The Chairman wishes to state that highly satisfactory reports were received from the Preceptors.

"Two of the above six 1951-52 Research Fellows relinquished their fellowships, which had been held in reserve for them due to military duty, and thus the funds previously held in reserve for them have been returned to the Research Fellowship Reserve Fund (Dr. John William Athens, \$3,500.00; Dr. James Edwin Wood, III, \$3,500.00). The sixth Research Fellow in the 1951-52 group is still on military service, but expects to be released from active duty probably during April, 1953, and then plans to take up the Fellowship which has been held in reserve for him (Dr. Sidney Harold Ingbar—to work at Thorndike Memorial Laboratory under Dr. Maxwell Finland).

"The Committee desires to report that the following 1952-53 Research Fellows started work on schedule, July 1, 1952:

1. Dr. Calvin Ezrin (Alfred Stengel Research Fellow)

\$4,000.00; University of Toronto School of Medicine, Dr. Ray F. Farquharson, Preceptor; field, effect of severe malnutrition from various causes on endocrine structure and function.

2. Dr. Thomas William Fyles

\$3,000.00; McGill University Clinic, Royal Victoria Hospital, Dr. Bram Rose, Preceptor; field, effect of ACTH and Cortisone on asthma.

3. Dr. Ladd Watts Hamrick, Jr.

\$3,000.00; Duke Hospital, Dr. J. D. Myers, Preceptor; field, splanchnic blood flow and metabolism.

4. Dr. Avard Marion Mitchell

\$3,000.00; Peter Bent Brigham Hospital, Dr. Samuel A. Levine, Preceptor; field, cardiovascular diseases.

"From a list of twenty-five (25) applicants for the Research Fellowships for 1953-54, the following were selected:

1. **Dr. Arthur R. Anderson, Jr.**; age 33; a graduate of Vanderbilt University School of Medicine, 1950; to work under Dr. Beverly T. Towery, Vanderbilt University School of Medicine, Nashville, Tenn., to study the quantitative estimation of urinary iodide excretion in normal individuals and in patients with thyroid disease; \$3,500.00.

2. **Dr. Frederick William Dick**; age 33; a graduate of Duke University School of Medicine, 1949; to work under Dr. C. Lockard Conley, Hematology Division of Department of Medicine, Johns Hopkins University, Baltimore, Md., on studies to be carried out on patients with hemorrhagic disorders in order to learn more about the

nature of certain of these disorders and at the same time to gain information concerning normal hemostatic mechanisms; \$3,500.00.

3. *Dr. William Stribling Dingledine*; age 27; a graduate of University of Virginia Department of Medicine, 1951; to work under Dr. John B. Stanbury, Thyroid Clinic, Massachusetts General Hospital, Boston, Mass., on the physiology of the thyroid, especially in its ramifications with respect to heart disease; \$3,500.00. (This recipient later declined the award.)

4. *Dr. Bernard Jacob Haverback*; age 27; a graduate of Johns Hopkins University School of Medicine, 1950; to work under Dr. Thomas E. Machella, Gastro-intestinal Clinic, Hospital of the University of Pennsylvania, Philadelphia, to study the measurement of intraluminal pressure at various levels in the gastro-intestinal tract by means of a strain gauge apparatus; \$4,000.00.

5. *Dr. Chesterfield Garvin Gunn, Jr.*; age 32; a graduate of Yale University School of Medicine, 1950; to work under Dr. E. Grey Dimond in the Cardiovascular Laboratory, University of Kansas Medical Center, Kansas City, Kans., to study the influence of the central nervous system on experimentally produced hypertension; \$3,500.00.

6. *Dr. Gordon Melvin Mindrum*; age 33; a graduate of the State University of Iowa College of Medicine, 1950; to work under Dr. Leon Schiff, Department of Medicine, Cincinnati General Hospital, Cincinnati, Ohio, on a study of a high fat diet with various types of liver disease, including the studies of liver biopsies, liver function studies and clinical course; \$3,000.00.

7. *Dr. Gerald Howard Whipple*; age 29; a graduate of University of California Medical School, 1946; to work under Dr. Harold D. Levine, and, to a lesser degree, under Dr. Samuel A. Levine, Peter Bent Brigham Hospital, Boston, Mass., on a clinical and mathematical study involving the application of solid geometry and spherical trigonometry to facilitate the quantitative analysis of vectorcardiograms; \$3,500.00. (This recipient later declined the award.)

"The following candidate, *Dr. Bernard Jacob Haverback*, was selected from the above group to be designated as the 'Alfred Stengel Research Fellow,' on account of his outstanding qualifications.

"The above calls for a total appropriation of \$24,500.00. Because we have increased the number of fellowships to seven instead of six, this will require an additional appropriation of \$5,000.00, beyond the figure submitted in the Budget by the Executive Secretary. It is pointed out that a larger proportion than usual of the fellows selected are married, and that also has increased the necessary appropriation."

. . . On motion by Dr. Howard P. Lewis, seconded by Dr. Wallace M. Yater, and unanimously carried, the above seven Research Fellowships were approved and the additional Budget appropriation authorized. . . .

DR. STURGIS (continuing his report): "The Committee then discussed augmenting of fellowship funds, from outside sources, a problem which had not come up before, and it is the consensus of opinion of the Committee that we should not approve augmenting fellowship funds unless some most unusual circumstances prevailed, which should be decided in each instance."

DR. YATER, Chairman of the Committee on the Alfred Stengel Award, reported for that Committee and presented three nominations. Following a secret ballot, one of the nominees was selected, but his name shall not be announced until the Annual Convocation of the College at Atlantic City in April, 1953.

DR. MARTIN, as the Chairman of the Committee on Masterships, presented the recommendation that Masterships shall be conferred at the next Convocation upon DR. FRANCIS M. POTTENGER, SR., MONROVIA, CALIFORNIA, and DR. REGINALD FITZ, BOSTON, MASSACHUSETTS. The recommendation was approved unanimously by resolution.

Secretary Loveland presented the proposed Revision of the Fellowship Pledge as submitted by Dr. Reginald Fitz, Chairman of a Committee appointed a year ago for the purpose. The following Revision was by resolution unanimously approved.

REVISED FELLOWSHIP PLEDGE

"I appreciate that the American College of Physicians has been created to foster the best principles and traditions of our calling. I have voluntarily accepted membership in this College. I solemnly pledge that to the utmost of my ability I will live in conformity with its ideals and regulations.

"Now, therefore, I dedicate myself to practice medicine following the Golden Rule and the precepts of the Oath of Hippocrates; to place the welfare of my patients ever before my own; to respect the reputation of my colleagues; to supplement, as occasion requires, my own judgment with the wisdom and counsel of competent medical specialists; to render assistance willingly to my colleagues; to extend freely my professional aid to the unfortunate; to seek increase in medical knowledge by continuing study, by attendance at important gatherings of my professional brethren, by association with physicians of eminence and by free exchange of experience and opinion with my colleagues.

"Further, I will avoid commercialism in all my professional activities, I will refrain from seeking the public eye for purposes of self-advancement and I will ask fees commensurate with my services and adjusted to the circumstances of my patients.

"Finally, I condemn and will avoid all debasing money trades with brother practitioners. I will strive constantly to spread among all physicians the noble ethics of practice set forth in the Constitution and By-Laws of this College."

Dr. Bortz proceeded to present the report of the Committee on Public Relations. The first item covered reports from a number of members who have been concerned about the inequities in the fee schedules as set up by the Blue Shield in various parts of the country. These members have pointed out the numerous inequities in fees set up with special reference to the treatment of emergency conditions of a medical nature. For example, coronary occlusion or diabetic coma cases, requiring a considerable amount of time and skill, are paid on the basis of what a general practitioner receives, while surgical procedure of like seriousness carries a relatively higher fee. Dr. Bortz said the Committee, in line with the traditional activities added to the College, recommends that since the College has not interested itself in the commercial and economic side of medical practice, no action shall be taken. The Committee, however, did report that some members felt the College might have a Committee appointed at the local Governors' level, to be known as a Liaison Committee of the College, working with the Governor of a particular area, to communicate with the officials of the Blue Cross and Blue Shield in problems of fee adjustments. The Board of Regents, by resolution, voted not to establish such a Liaison Committee, since it has been the traditional attitude of the College not to take part in problems of an economic nature.

The second proposal presented through the Committee on Public Relations was the recommendation from Dr. Joseph D. McCarthy, College Governor for Nebraska, that a second joint meeting of the Regents and Governors be held at the Annual Sessions. It was pointed out that at present there is a joint meeting of the Regents and Governors on the day before the opening of the Annual Session and that thereafter there are stated meetings of the Regents and Governors for the transaction of the individual problems of those Boards, and that the only practical time to have a second joint meeting would be on the last day of the Session when the Board of Regents proceeds with the organization of Committees and other personnel for the coming year. In view of the fact that this proposal had come from but one Governor, a resolution was adopted referring the matter to the Board of Governors for con-

sideration to determine if they are really interested in an additional joint meeting with the Regents.

The next item discussed by Dr. Bortz was a suggestion regarding the adding of a full Scientific Exhibit at the Annual Session of the College. It was stated that the Board of Regents of the College on a previous occasion had voted adversely on the establishment of a Scientific Exhibit, believing that exhibitors should be encouraged to join in the Scientific Exhibit of the American Medical Association, making that the one great national and complete exhibit. The Committee on Public Relations made no recommendation and no action was taken.

Dr. Bortz then stated that the American Association of Medical Record Librarians had requested the College to appoint a representative to their Committee on Education and Registration. That organization has a representative already from the American College of Surgeons, from the American Heart Association and from the American Medical Association, to advise on matters of policy and terminology, etc. The Committee on Public Relations recommended that the Board of Regents agree to this representation and that the President make the appointment. It was approved by resolution.

Dr. Bortz then on behalf of his Committee presented a request for support from the World Medical Association through its Secretary-General. In 1951 the College contributed \$1,000.00, but has not seen fit to continue contributions since. After extended discussion, a resolution was adopted providing that the Board of Regents shall approve and publish that approval of the World Medical Association, with the recommendation that our members, if they are so inclined, join it. The resolution did not contain any provision for further donations by the College.

Dr. Bortz then presented a communication from Dr. A. J. Carlson, M.A.C.P., President of the National Society for Medical Research, soliciting a contribution by the College. Dr. Bortz indicated that this is a society that is fighting the anti-vivisectionists who are a real threat to medical research by animal experimentation. Dr. Bortz distributed literature supplied by Dr. Carlson, said that the College has supported this organization in the past, and that the Committee on Public Relations recommends that the College give its positive support. A motion was adopted authorizing a contribution of \$100.00.

On the recommendation of the Committee on Public Relations, the dues of a Fellow who has been incapacitated were waived, and the resignation of Dr. William H. Fusting, Baltimore, an Associate of the College, was accepted.

Dr. Bortz then presented a set of communications involving the accusation of plagiarism on the part of one of the College members. After extended discussion, the matter was placed in the hands of Dr. Asa L. Lincoln, a member of the Board of Regents, for detailed study and investigation, a report to be made at the next meeting of the Board of Regents.

No formal report was available from the Committee on the Annals of Internal Medicine due to the absence of Dr. Alex. M. Burgess, Chairman, who was ill.

Dr. Bortz was requested, as Acting Chairman, to make a report for the Committee on Educational Policy.

DR. BORTZ: "At the last meeting of our Committee on Educational Policy, there was a recommendation made that apparently was not clear to the Board of Regents, and, therefore, Dr. Marion A. Blankenhorn, who is Chairman of our Committee, drew up another recommendation in its place, reading as follows:

"Resolved, that the Committee on Educational Policy be enlarged to five in number; that the Committee be relieved of duty with the Committee on Postgraduate Courses and be instructed to undertake, with the aid of the Executive Secretary, a systematic collection of the evidences of membership satisfaction or dissatisfaction with the program at the Annual Session; that the Committee study these evidences by

special meeting, if need be, and submit a report as promptly as possible to the Consulting Committee on Annual Sessions.

"This is the new recommendation, which is in accord with the suggestions of past President Dr. Maurice C. Pincoffs. There are two things: in the first place, the recommendation divorces the Committee on Educational Policy from the Committee on Postgraduate Courses; second, it proposes to enlarge the Committee to five members, with the designated assignment of studying the membership reaction to the programs of Annual Sessions. The Committee offers this as a resolution."

. . . The motion was duly seconded, put and carried. . . .

Dr. Thomas M. McMillan, Chairman of the Governors' Committee on Post-graduate Courses, reported in great detail. Among the highlights of his report, he reviewed the entire Postgraduate Course Program for the year 1952, and said that while some courses were not largely attended, they were thoroughly worthwhile and the comments of those who attended were most enthusiastic. He reminded the Regents that the worth and value of the courses are not necessarily to be measured by attendance. The total attendance for the Spring, 1952 Courses was 474, and for the Autumn, 1952 Courses, he predicted an attendance of about 600, making the total enrollment for the year about 1,100. Dr. McMillan particularly spoke with praise of three new courses that had appeared on the program in 1952, namely: TRENDS AND NEWER DEVELOPMENTS IN INTERNAL MEDICINE, by Dr. Charles L. Brown, Director, Hahnemann Medical College and Hospital of Philadelphia; PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE, by Dr. Ray F. Farquharson, Director, University of Toronto Faculty of Medicine; and RECENT TRENDS IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE, by Drs. Arthur M. Master and Charles K. Friedberg, Directors, at Mount Sinai Hospital, New York City.

Dr. McMillan then presented the following Schedule of Courses for the Spring of 1953:

- No. 1, PATHOLOGY AND PATHOLOGIC PHYSIOLOGY IN INTERNAL MEDICINE: Frank E. Bunts Educational Institute of the Cleveland Clinic Foundation, Cleveland, Ohio; A. Carlton Ernstene, M.D., F.A.C.P., Director. February 16-21, 1953.
- No. 2, STUDIES IN THE CLINICAL ASPECTS AND DIAGNOSTIC PROCEDURES IN CARDIOVASCULAR DISEASE: University of Southern California School of Medicine, Los Angeles, Calif.; George C. Griffith, M.D., F.A.C.P., Director. March 2-7, 1953.
- No. 3, INTERNAL MEDICINE; SELECTED SUBJECTS: Cornell University Medical College and the New York Hospital, New York, N. Y.; David P. Barr, M.D., F.A.C.P., Director. March 9-13, 1953.
- No. 4, INTERNAL MEDICINE: Mayo Clinic and Foundation, Rochester, Minn.; Drs. Arlie R. Barnes, Hugh R. Butt, Edgar V. Allen and William H. Dearing (all F.A.C.P.), Co-Directors. March 23-28, 1953.
- No. 5, CARDIOVASCULAR DISEASE: Philadelphia Institutions, Philadelphia, Pa.; William G. Leaman, M.D., F.A.C.P., Director. April 27-May 2, 1953.
- No. 6, CONTROVERSIAL ISSUES IN INTERNAL MEDICINE: The Pennsylvania Hospital, Philadelphia, Pa.; Garfield Duncan, M.D., F.A.C.P., Director. May 11-15, 1953.
- No. 7, ELECTROCARDIOGRAPHY: BASIC PRINCIPLES AND INTERPRETATION: Massachusetts General Hospital, Boston, Mass.; Conger Williams, M.D. (Associate), Director. May 11-16, 1953.
- No. 8, INTERNAL MEDICINE; IMPORTANT REFINEMENTS OF DIAGNOSIS AND TREATMENT: University of Oregon School of Medicine, Portland, Ore.; Howard P. Lewis, M.D., F.A.C.P., Director. May 18-22, 1953.

Dr. McMillan then presented the following proposed schedule of Courses for the Autumn of 1953:

"Autumn, 1953, Courses:

- No. 1. RHEUMATIC DISEASES
Massachusetts General Hospital, Boston, Mass.; Walter Bauer, M.D., F.A.C.P., Director.
- No. 2. INTERNAL MEDICINE
University of Wisconsin Medical School, Madison, Wis.; William S. Middleton, M.D., M.A.C.P., and Karver L. Puestow, M.D., F.A.C.P., Co-Directors.
- No. 3. INTERNAL MEDICINE
Vanderbilt University School of Medicine, Nashville, Tenn.; Rudolph Kampmeier, M.D., F.A.C.P., Director.
- No. 4. HEMATOLOGY
Northwestern University Medical School, Chicago, Ill.; Howard L. Alt, M.D., F.A.C.P., Director; Dr. Leon O. Jacobson, F.A.C.P., Co-Director; Louis R. Limarzi, M.D., F.A.C.P., Co-Director.
- No. 5. CARDIOLOGY
Massachusetts General Hospital, Boston, Mass.; Howard B. Sprague, M.D., F.A.C.P., and Edward F. Bland, M.D., F.A.C.P., Co-Directors.
- No. 6. CLINICAL NEUROLOGY
Jefferson Medical College of Philadelphia, Philadelphia, Pa.; Bernard A. Alpers, M.D., F.A.C.P., Director.
- No. 7. Some course on a phase of Internal Medicine (the exact title to be decided upon) at Columbia University College of Physicians and Surgeons, New York, N. Y.; Franklin Hanger, M.D., F.A.C.P., Director. If the Board of Regents sees fit to approve this course, we will attempt to arrange it.
- No. 8. PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE
To be directed by Julius H. Comroe, Jr., M.D., F.A.C.P.
- No. 9. APPLIED PHARMACOLOGY AND THERAPEUTICS
To be jointly directed by Maxwell M. Wintrrobe, M.D., F.A.C.P., and Louis S. Goodman, M.D., of the University of Utah College of Medicine.

"It will be noted that the scheduled courses for the fall of 1953 contain several new Directors, and at least one course which is quite different than any given before, and at least one course (Course No. 9) on a subject which has never been undertaken before. The Committee on Postgraduate Courses, as well as the advisers from the Committee on Educational Policy, feel that we should probe new fields and frontiers of medicine. This is the reason for the subject of the last course on our schedule. In line with this desire to attempt something different, the Committee on Postgraduate Courses has decided upon two new courses which will not be scheduled for some time. Our Committee is particularly anxious for the Regents to know of these new courses. We hope that they will approve of our scheduling them even though the giving of these courses will be decidedly an experiment. The courses are:

- No. 1. BASIC PROBLEMS OF NEOPLASIA
To be given at the Memorial Hospital, New York, N. Y. One reason why this course was selected is that the study of malignancy has seemed to have passed some of those interested in internal medicine, and our Committee feels that it is quite likely that the members of the College may well wish to renew and expand their knowledge of this important subject.
- No. 2. A three-day course in BALLISTOCARDIOGRAPHY
Probably would be given at the University of Rochester under the direction of Dr. Herbert R. Brown (Associate). The latter course is recommended.

because we know that Ballistocardiography is being extensively applied and that its application will increase. It is known, for example, that one company has sold no less than five thousand instruments. Since many are using this method who are not able to use it properly, the Committee feels that we should handle it exactly as we have handled Electrocardiography, and do our best to see that those of our members who will use the method have a good opportunity to learn to use it correctly.

"Possible Courses to be given in the future:

ELECTROCARDIOGRAPHY

Wayne University College of Medicine, Detroit, Mich.; Gordon B. Myers, M.D., F.A.C.P., Director.

CARDIOLOGY

New York University-Bellevue Medical Center, New York, N. Y.; J. Scott Butterworth, M.D., F.A.C.P., or Clarence E. de la Chapelle, M.D., F.A.C.P., or Charles Kossmann, M.D., F.A.C.P., Director.

CRITICAL PROBLEMS IN INTERNAL MEDICINE

University of Chicago School of Medicine, Chicago, Ill.; Wright Adams, M.D., F.A.C.P., Director.

INTERNAL MEDICINE

University of Southern California School of Medicine, Los Angeles, Calif.; Paul Starr, M.D., F.A.C.P., Director.

INTERNAL MEDICINE

University of Chicago School of Medicine, Chicago, Ill.; Lowell T. Coggesshall, M.D., F.A.C.P., Director.

INTERNAL MEDICINE

University of Cincinnati College of Medicine, Cincinnati, Ohio; Marion A. Blankenhorn, M.D., F.A.C.P., Director.

INTERNAL MEDICINE

Temple University School of Medicine, Philadelphia, Pa.; Thomas M. Durant, M.D., F.A.C.P., Director.

HEMATOLOGY OR INTERNAL MEDICINE

Boston, Mass.; Maurice Strauss, M.D., F.A.C.P., Director.

HEMATOLOGY

Ohio State University College of Medicine, Columbus, Ohio; Charles A. Doan, M.D., F.A.C.P., Director.

HEMATOLOGY

Washington University School of Medicine, St. Louis, Mo.; Carl V. Moore, M.D., F.A.C.P., Director.

CARDIOLOGY

Michael Reese Hospital, Chicago, Ill.; Louis N. Katz, M.D., F.A.C.P., Director.

PERIPHERAL VASCULAR DISEASES, INCLUDING HYPERTENSION

Mayo Foundation, Rochester Minn.; Edgar V. Allen, M.D., F.A.C.P., Nelson W. Barker, M.D., F.A.C.P., et al., Co-Directors.

GASTRO-ENTEROLOGY

New Orleans Institutions, New Orleans, La.; G. Gordon McHardy, M.D., F.A.C.P., Director.

ENDOCRINOLOGY

Tufts College Medical School, Boston, Mass.; Edwin B. Astwood, M.D., F.A.C.P., Director.

LIFE STRESS AND BODILY DISEASE

Cornell University Medical College and the New York Hospital, New York, N. Y.; Harold G. Wolff, M.D., F.A.C.P., Director.

PHYSICAL MEDICINE

New York University College of Medicine, New York, N. Y.; Howard A. Rusk, M.D., F.A.C.P., Director.

"For a number of years, the possibility of giving a three-day course has been discussed, but no action taken. In the opinion of a number of persons, many physicians who cannot give the time for a five-day course would give the time for a three-day course. We, of course, cannot be sure of this, and the only way to discover the truth is to try such a course. Ballistocardiography is undoubtedly an almost new subject, concerning which there is much interest; one manufacturer alone has sold five thousand Ballistocardiographs. Since this is a subject which requires training and experience, our Committee feels that it should be handled just as the College is handling Electrocardiography and that we should do our part to make it possible for our Fellows to receive sound training. At some time in the future, therefore, our Committee would like very much to ask approval of a course in Ballistocardiography.

"Our Committee discussed the fact that Neoplasia, in general, has largely passed out of the hands of internists. Our Committee feels that a broad course on the subject of Neoplasia might be an important course for the College to provide."

. . . On motion duly seconded, put and carried, the report and recommendations of the Committee on Postgraduate Courses were approved. . . .

President Miller then called for the report of the Committee on Finance by Dr. A. B. Brower, Chairman.

Dr. Brower reported that all members of the Committee and the Executive Secretary had met with representatives of the Investment Counselors of the College, Drexel and Company, to discuss the College investment policies and the present portfolio. He then presented a detailed report of all purchases and sales of securities, both in the General Fund and in the Endowment Fund, since the last meeting of the Board of Regents. On recommendation of the Committee on Finance, the Board of Regents approved the appropriation of \$389.00 for publication of "Abstracts" for the Midwest Regional Meeting, held at Chicago, November 22, 1952.

Dr. Brower then presented the list of security transactions recommended by Drexel and Company, amounting approximately to \$87,000.00. These recommendations were approved by the Board of Regents as was also authority for the Treasurer to invest surplus funds of possibly \$50,000.00 on or about February 1, 1953, in short term securities, namely, 90-day United States Bills.

Dr. Brower then presented the statements of operation for the year 1952 (figures for October through December estimated), showing an estimated surplus at the end of 1952 of \$69,000.00 in the General Fund. Budget comparisons for the year 1951 showed that the College operated essentially within its Budget, and that the income exceeded expectations by some \$47,000.00.

Dr. Brower also presented a three-year comparison of operating costs for the *ANNALS OF INTERNAL MEDICINE*. Income from subscriptions was slightly higher in 1952 than in 1951, but advertising income increased by some \$12,000.00. Printing and publication costs remained more or less stable; surplus from the publication of the journal increased about \$9,000.00 over the previous year, to \$67,700.00.

Dr. Brower further presented an analysis of Annual Session costs, and a three-year comparison. He pointed out that expenses vary from year to year according to meeting place and local conditions. The 1952 Annual Session in Cleveland was far more expensive than the previous Annual Session in St. Louis, because of increased costs of rental of auditorium and the building of special meeting rooms, increase of costs of women's entertainment and an extra expense for the building of the Butterworth Scientific Exhibit. However, the income from exhibits and guest fees was the highest on record and covered all the expenses of the Annual Session with the exception of about \$1,500.00.

Dr. Brower then presented the Budget for 1953, which was gone over with care and with detailed explanations. A recapitulation of the Budgets approved by the Regents provides for an estimated income during 1953 of \$356,490.00, and total estimated expenditures of \$293,000.00.

President Miller then called upon the Secretary-General, Dr. Richard A. Kern, who also serves as Chairman of the College Committee on Military Affairs, for a report. Dr. Kern had attended, on behalf of the College, a meeting of the Council on National Emergency Medical Service of the American Medical Association shortly before the current meeting of the Board of Regents. Attending said meeting were representatives from the Armed Forces, including the Office of the Secretary of Defense, the three Surgeons General, Army, Navy and Air Force, the Surgeon General of the Public Health Service, representatives of other government groups, including the Veterans Administration, and representatives from the American Medical Association, the Student American Medical Association, the American Academy of General Practice, the American College of Surgeons, the American Dental Association, the American Drug Manufacturers Association, the American Hospital Association, the American Veterinary Medical Association and State and Territorial Health Officers. The purpose of the session was to discuss the status of the Doctor Draft Law, the question of needs for its replacement since that Law lapses on July 1, 1953, and if there be need for a new Law, what kind of a Law should take its place. Dr. Kern went into great detail, and discussed the numerous considerations and problems involved. The report is of such length that it does not appear appropriate to publish it at this time, but the contents may be obtained by members of the College who may be affected or interested.

President Miller then called upon Dr. A. B. Brower, Chairman of the Committee on Insurance, for a report. The Secretary passed around the detailed data on which the report was based.

DR. BROWER: "Mr. President, members of the Board of Regents, I first would like to say that Mr. Loveland did a most extensive research concerning this whole matter. As a matter of fact, without his extensive research and follow-up of these various subjects, I am sure that the Committee could not have arrived at any real and definite conclusion.

"Your Committee, composed of Dr. J. Owsley Manier, Dr. Walter B. Martin, and myself, and Mr. Loveland, met at the College Headquarters from 2 p.m. until 5:45 p.m. on November 14, and we were fortunate in having Mr. F. Wells McCormack sit in with us a part of the time to answer questions.

"The Committee by unanimous resolution recommends to the Board of Regents:

- (1) That the American College of Physicians shall adopt a Plan of Health and Accident Insurance presented by the Educators Mutual Insurance Company, Lancaster, Pa., as embodied in a formal proposal herewith delivered to the Secretary, and also a proposal for Group Professional Liability Insurance, some details of which are yet to be concluded."

. . . On motion by Dr. A. B. Brower, duly seconded, put and carried, this recommendation was approved. . . .

DR. BROWER (continuing): "Now, Mr. President, since the first recommendation is approved by the Board, then the Committee recommends that Messrs. F. Wells McCormack and Ralph O. Claypoole, whose business and office are already established in Philadelphia and who are already the College brokers for its Pension Plan, shall be appointed as the official broker of the College."

. . . On motion by Dr. A. B. Brower, seconded by Dr. Walter B. Martin, put and carried, this recommendation was approved. . . .

DR. BROWER (continuing): "The Committee further believes it appropriate that the Board of Regents authorize the Executive Secretary of the College and the broker to proceed with the detailed announcement of the Plan and to initiate the necessary procedures at a suitable time, and I so move."

. . . The motion was duly seconded by Dr. J. Owsley Manier, put and carried. . . .

President Miller then reviewed in some detail the plans for the next Annual Session of the College in Atlantic City in April. He spoke at some length concerning the program of Symposia and General Sessions. He proposed that the College invite as guests to dinner on Sunday evening, April 12, at the Atlantic City Annual Session all newly elected Associates and all newly elected Direct Fellows for the purpose of making them welcome in the College and to give them an opportunity to become acquainted with each other and with the Boards of the College. He pointed out that those invited obviously would be those elected at the November, 1952 meeting of the Board of Regents, and could not include those who will be elected at the Annual Session, because of inadequate time available to notify them in advance. They will be accommodated at the next succeeding Annual Session.

Dr. Hilton S. Read, as General Chairman, made an extended report of the program for which he has been responsible, delineating the different types of program, moderators and contributors and entertainment features.

The Board of Regents by unanimous action approved the recommendation of President Miller with regard to the entertainment of the newly elected members and made an appropriation of \$2,100.00 therefor. The Board also appropriated a sum of \$3,000.00 for general entertainment to be used by the General Chairman of the Annual Session.

President Miller announced that the next meeting of the Committee on Credentials will be held at the Philadelphia Headquarters on March 8, 1953, and that the next succeeding meeting of the Board of Regents will be held at Atlantic City, New Jersey, on April 12, 1953, the meeting to be held in conjunction with the Board of Governors.

Adjournment.

Attest: E. R. LOVELAND,
Secretary

PROGRAM
THE AMERICAN COLLEGE OF PHYSICIANS
Thirty-fourth Annual Session
ATLANTIC CITY, N. J.
April 13-17, 1953

GENERAL SESSIONS AND SYMPOSIA

T. Grier Miller, Philadelphia, Pa., President

COMMITTEE ON ARRANGEMENTS

Hilton S. Read, General Chairman

Clarence B. Whims, Assistant General Chairman

Clarence L. Andrews

Clifford K. Murray

Harold S. Davidson

Samuel L. Salasin

Robert B. Durham

D. Ward Scanlan

Matthew Molitch

Sloan G. Stewart

COMMITTEE ON AUDITORIUM

Sloan G. Stewart, Chairman

Milton Cutler

James F. Gleason

COMMITTEE ON CLINICAL PATHOLOGICAL CONFERENCES

Harold S. Davidson, Chairman

Peter A. Herbut, Co-Chairman

Milton Ackerman

Robert Bruce Nye

Edward L. Bortz

Henry J. Tumen

William A. Jeffers

Frederick O. Zillessen

COMMITTEE ON ENTERTAINMENT

Robert B. Durham, Chairman

Russell S. Boles

William W. Fox

Aldrich C. Crowe

Merle M. Miller

COMMITTEE ON HOTELS

Clarence L. Andrews, Chairman

James F. Gleason

COMMITTEE ON PANEL DISCUSSIONS

Clifford K. Murray, Chairman

Louis B. Laplace, Co-Chairman

Bernard J. Alpers

John Lansbury

Henry L. Bockus

Pascal F. Lucchesi

W. Edward Chamberlain

Peter H. Marvel

Julius H. Comroe, Jr.

Malcolm W. Miller

Joseph F. Hughes

Edward B. Tyson

Edward Weiss

COMMITTEE ON PUBLICITY

D. Ward Scanlan, Chairman

Calvin F. Kay

Irving C. Shavelson

Henry F. Page

Louis A. Soloff

John H. Willard

COMMITTEE ON TELEVISED CLINICS

Matthew Molitch, Chairman

Kendall A. Elsom, Co-Chairman

J. Edward Berk

O. Spurgeon English

Mitchell Bernstein

Lowell A. Erf

Charles L. Brown

Burgess L. Gordon

Paul Cutler

William G. Leaman

Thomas M. Durant

Abraham M. Ornsteen

Eugene P. Pendergrass

COMMITTEE ON TRANSPORTATION

Samuel L. Salasin, Chairman

Sidney Rosenblatt

COMMITTEE ON LADIES' ENTERTAINMENT

Mrs. T. Grier Miller, Honorary Chairman

Mrs. Clarence B. Whims, Chairman

Mrs. Richard A. Kern

Mrs. Clifford K. Murray

Mrs. Peter H. Marvel

Mrs. Hilton S. Read

Mrs. Malcolm W. Miller

Mrs. William D. Stroud

GENERAL INFORMATION**GENERAL HEADQUARTERS****Atlantic City Convention Hall**

Registration headquarters, the information bureau, technical exhibits, general sessions, morning symposia, panel discussions, clinical-pathological conferences, televised clinics, "Meet the Expert" lectures, meetings of Committees, of the Board of Regents and of the Board of Governors. The Annual Convocation will be held in the Ballroom of Convention Hall, but the Annual Banquet will take place in the Chalfonte Hotel.

HOTEL ACCOMMODATIONS

Atlantic City Hotels provide far more rooms than are actually required for the Annual Session of the College. Therefore, it has not been necessary to set up a Housing Bureau. Members and guests may use an official reservation form, prepared by the Atlantic City Convention Bureau, and apply to any hotel of their choice. The American Heart Association will hold its meeting in Atlantic City, with headquarters at the Chelsea Hotel, April 8-12. The headquarters hotel of the American College of Physicians is the Haddon Hall and Chalfonte. A hotel reservation form has been devised for use by both organizations, because there is a great overlapping of the membership. By using this form and making a reservation for the entire period of both Conventions, one may prevent the necessity of having to move from one hotel to another between meetings. Reservation forms will accompany the formal program mailed to all members during early February. Additional copies may be obtained from the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa.

LIST OF HOTELS

BOARDWALK HOTELS

Hotels	Total rooms	Rooms with Bath		Two Rooms—One Bath			Room and Parlor	
		Single	Double	2 Persons	3 Persons	4 Persons	Single	Double
Ambassador.....	670	6.00-14.00	8.00-18.00	12.00	16.00-25.00	16.00-25.00		20.00-36.00
Breakers.....	475	5.00- 9.00	7.00-14.00		10.00-18.00	12.00-21.00		
Brighton.....	291	6.00-10.00	8.00-14.00		18.00	22.00		18.00-28.00
Chalfonte—								
Haddon Hall.....	1000	6.00-20.00	9.00-22.00					24.00-42.00
Chelesa.....	400	5.00-11.00	7.00-16.00		12.00	15.00-18.00		24.00-30.00
Claridge.....	406	7.00-15.00	11.00-19.00					36.00
Dennis.....	475	6.00-12.00	9.00-20.00		15.00-18.00	22.00-26.00		27.00-34.00
Marlborough—								
Blenheim.....	464	6.00- 9.00	9.00-18.00	15.00-17.00	15.00-19.00	17.00-22.00		27.00-36.00
Mayflower.....	280	6.00-11.00	8.00-14.00		13.00-17.00	16.00-20.00		
New Belmont.....	100	4.00- 5.00	6.00-10.00		12.00-14.00	13.00-16.00		
President.....	500	5.00-10.00	8.00-18.00					19.00-24.00
Ritz-Carlton.....	431	6.00- 8.00	8.00-16.00			20.00		25.00-35.00
Seaside.....	235	6.00-11.00	8.00-14.00					28.00
Shelburne.....	300	6.00-16.00	9.00-18.00					39.00-50.00
Traymore.....	600	6.00-14.00	8.00-18.00					20.00-45.00

AVENUE HOTELS

Hotels	Total rooms	Rooms with Bath		Two Rooms—One Bath			Rooms without Bath	
		Single	Double	2 Persons	3 Persons	4 Persons	Single	Double
Roscobel.....	120	3.00- 4.00	6.00- 7.00		9.00	10.00-12.00	2.00-2.50	3.50- 4.00
Carolina Crest.....	73	5.00- 7.00	7.00-10.00					
Clarendon.....	100	5.00- 6.00	7.00			12.00	3.50	5.00
Coltton Manor.....	208	7.00-10.00	9.00-14.00	12.00	15.00	18.00		
Columbus.....	100		6.00- 8.00			12.00-16.00		5.00- 6.00
Crillon.....	49		8.00-10.00					
Eastbourne.....	100	5.00- 8.00	7.00-10.00	10.00-12.00	12.00-14.00	14.00-16.00	3.00-4.00	5.00- 6.00
Flanders.....	125	5.00- 6.00	7.00-10.00			16.00	4.00	6.00
Fox Manor.....	60	5.00- 8.00	6.00-12.00	8.00-10.00	10.00-15.00	12.00-20.00	4.00-6.00	5.00- 8.00
Holmhurst.....	100		7.00- 8.00			14.00	3.00	4.00
Jefferson.....	150	5.50- 8.00	7.00-10.00			12.00-20.00		4.00- 6.00
Kentucky.....	110	3.50	6.00- 7.00	7.00	10.00	10.00-12.00	2.00-2.50	4.00- 5.00
Lafayette.....	215	5.00- 8.00	8.00-14.00	10.00-12.00		16.00-20.00		1 Double & Bath
Lexington.....	100	5.00	6.50- 8.50	9.00	11.00	12.00-14.00	3.00-4.00	4.50- 6.50
Madison.....	210	6.00- 8.00	7.00-12.00		12.00-16.00	14.00-20.00	4.00	6.00
Monticello.....	175	4.00	7.00			11.00-14.00	2.00-3.00	3.50- 5.00
Morton.....	300	5.00- 7.00	7.00-10.00			12.00-14.00		
Penn-Atlantic.....	140		7.00-10.00					
Runnymede.....	75	4.00- 7.50	6.00-10.00					
Senator.....	260	5.00- 7.00	7.00-12.00	10.00	15.00	16.00-18.00	3.00-4.50	5.00- 7.00
Sterling.....	83	6.00- 7.00	8.00-10.00				4.00	6.00- 7.00
Villa D'Este.....	40	4.00- 7.00	6.00-10.00					

Who May Register—

- (a) All members of the American College of Physicians in good standing for 1953.
- (b) All newly elected members.
- (c) Members of the staff, including interns, residents and graduate medical students, of the Atlantic City and Shore Memorial Hospitals, without registration fee, upon presentation of proper identification: admission to exhibits, general sessions, morning symposia and TV clinics.
- (d) Graduate medical students pursuing courses in Philadelphia medical schools, without registration fee, upon presentation of matriculation cards, or other evidence of registration at these institutions: admission to exhibits, general sessions, morning symposia and TV clinics.
- (e) Bona fide hospital residents, regardless of their location in North America, without registration fee, upon presentation of proper credentials from their hospitals: admission to exhibits, general sessions, morning symposia, and other program features where facilities are adequate.
- (f) Members of the Medical Corps of the Army, Navy, Public Health Service, Air Force and Veterans Administration, either of the United States or Canada, without registration fee, upon presentation of proper credentials.
- (g) Qualified physicians who may wish to attend this Session as visitors, sponsored in advance by letter or in person by a member of the College; such physicians shall pay a registration fee of \$25.00, this entitling them to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published).

The above regulations are essential because of the increasingly large attendance at the Annual Sessions of the College, and the necessity of accommodating members first.

Registration Bureau—While official registration will start on Monday morning, April 13, advance registration of members and exhibitors will be provided for on Sunday, April 12, from 2:30 P.M. to 5:00 P.M. The Registration Bureau, located in Convention Hall, will be open throughout the week from 8:45 A.M. to 5:30 P.M.

Registration Blanks for all Panel Discussions, Clinical-Pathological Conferences and "Meet the Expert" Lectures will be enclosed with the final program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

Bulletin Board for special announcements will be located near the Registration Bureau at Convention Hall.

Transportation—Local transportation arrangements are in charge of the Committee on Transportation, which will issue full information at the meeting. However, Hotels Haddon Hall and Chalfonte have agreed to operate throughout the week, for their guests, continuous free bus service between those hotels and Convention Hall.

The Annual Business Meeting of the College will be held from 2:00 P.M. to 2:40 P.M., Thursday, April 16, immediately preceding the afternoon scientific session. All Masters and Fellows of the College are urged to be present. There will be the election of Officers, Regents and Governors, the annual reports of the Secretary-General, Executive Secretary and Treasurer. The President-Elect, Dr. LeRoy H. Sloan, Chicago, will be inducted into office.

BOARD AND COMMITTEE MEETINGS

All meetings will be held at the Regents' and Governors' Headquarters in Convention Hall. Special meetings will be announced and posted.

A Reception and Dinner will be tendered by the Officers, Regents and Governors to those Associates and Direct Fellows so elected at the meeting of the Board of Regents on November 16, 1952; Haddon Hall, Sunday, April 12, 6:30 P.M.

Committee on Nominations

(At the call of the Chairman)

Committee on Credentials

Saturday, April 11, 10:00 A.M., Regents'-Governors' Room
Convention Hall

Committee on Fellowships and Awards

Sunday, April 12, 10:00 A.M., Regents'-Governors' Room
Convention Hall

Committee on Insurance

Sunday, April 12, 10:00 A.M., Executive Secretary's Office
Convention Hall

Committee on Finance

Sunday, April 12, 11:15 A.M., Executive Secretary's Office
Convention Hall

Joint Meeting: Board of Regents and Board of Governors

Sunday, April 12, 2:00 P.M., Regents'-Governors' Room
Convention Hall

Committee on Educational Policy

Monday, April 13, 10:00 A.M., Regents'-Governors' Room
Convention Hall

Committee on Postgraduate Courses

Monday, April 13, 10:00 A.M., Executive Secretary's Office
Convention Hall

Committee on Public Relations

Monday, April 13, 11:00 A.M., Regents'-Governors' Room
Convention Hall

Committee on the Annals of Internal Medicine

Monday, April 13, 12:00 M., Regents'-Governors' Room
Convention Hall

Inspection, Committee on Technical Exhibits

Monday, April 13, 10:30 A.M., starting from the Executive
Secretary's Office, Convention Hall

Meeting, Technical Exhibitors

Monday, April 13, 5:20 P.M., Regents'-Governors' Room
Convention Hall

Board of Regents

- * Tuesday, April 14, 12:00 M., Regents'-Governors Room
- * Friday, April 17, 12:00 M., Regents'-Governors' Room
Convention Hall

Board of Governors

- * Wednesday, April 15, 12:00 M., Regents'-Governors' Room
Convention Hall

Annual Business Meeting

Thursday, April 16, 2:00 P.M., Ballroom, Convention Hall

SPECIAL FEATURES

Reception and Dinner, tendered by Officers, Regents and Governors of the College to new Associates and Direct Fellows: Haddon Hall, Sunday, April 12, 6:30 P.M.—The Officers, Regents and Governors of the College have arranged a Reception and Dinner for all the new Associates and Direct Fellows who were elected November 16, 1952, for the purpose of welcoming them to the College and to provide an opportunity to meet them personally and for them to meet one another. Special invitations will be issued by mail in advance of the Annual Session.

If this plan is adopted as a regular feature in the future, in 1954 such a Reception and Dinner will be tendered to all the Associates and Direct Fellows elected at the Atlantic City Session and at the succeeding meetings of the Board of Regents during 1953.

Concert, Philadelphia Orchestra, Sunday evening, April 12, 9:00 P.M., Warner Theater, Boardwalk—The Committee on Entertainment is gratified to announce this Concert by the great Philadelphia Orchestra, under the direction of Dr. Eugene Ormandy. The Philadelphia Orchestra is famous in this country and abroad. Not for many years has the College been able to offer such a wonderful entertainment feature. The Schering Corporation, of Bloomfield, N. J., has graciously provided the funds to make this Concert available to us.

Admission is free to all members and duly registered guests, to the exhibitors, and to the families of the same. Complimentary tickets will be issued at the Registration Bureau. Those arriving in Atlantic City late will be admitted at the door on any suitable identification.

Golf Tournament, Sunday, April 12, 11:00 A.M., Seaview Country Club—The famous pine tree sheltered course; no entry fee; prizes.

Trap Shooting Tournament, Sunday, April 12, 12:00 M.—The Westy Hogan Trap Shooting Club; no entry fee; guns provided, when requested; prizes.

Special Entertainment, Monday evening, April 13, 9:00 P.M., Ballroom, Convention Hall—An evening of divertissement with stars from radio, television, screen and stage. Admission free by ticket or badge.

The Annual Convocation and President's Reception, Wednesday evening, April 15—The Annual Convocation of the College will be held at 8:30 P.M. in the Ballroom of the Convention Hall. All members of the College and their families,

* Buffet luncheon served.

and those of the public who are interested, are cordially invited. No tickets will be required. All physicians elected Fellows of the College since the 1952 Convocation and all previously elected Fellows who have not been formally inducted should be present. Officers, Regents and Governors and new Fellows to be inducted, are requested to assemble on the Ballroom floor, south corridor (rear of Ballroom Stage) at 7:45 P.M., preparatory to the formation of the procession. Regents and Governors will assemble in Room 10. The Marshal and his Aides will direct the candidates to the proper location.

The Convocation ceremony will include the President's Address and the Convocational Oration by Roger I. Lee, M.D., M.A.C.P., Boston, Mass. The John Phillips Memorial Medal for 1953, the James D. Bruce Memorial Medal for 1953 and the Alfred Stengel Diploma for 1953 will be awarded. Recipients of Research Fellowships and Latin-American Fellowships of the College for 1953 and the two A. Blaine Brower Traveling Scholarships for 1953 will be announced, and two Masterships will be conferred upon distinguished members of the College. The class of new Fellows will be inducted by the President.

Following the Convocation the President's Reception and Ball will be held at Haddon Hall.

THE ANNUAL BANQUET, Thursday, April 16, 8:00 P.M.—At 7:00 P.M. there will be a "Dutch Treat" Cocktail Party and Reception, to be followed at 8:00 P.M. by the Annual Banquet in the Carolina Room, Hotel Chalfonte. The Entertainment Committee proposes to arrange seating in advance and to provide seat finders. Advance reservations are encouraged; reservations will be closed Wednesday morning; tickets will be on sale at the Registration Bureau. Table reservations for groups may be arranged. Speaker, Luther M. Schaeffer, Northampton, Pa., "The Superstitions of the Pennsylvania Dutch." Music by The Vikings, America's premier men of song.

Special Cardiac Exhibit and Demonstration—(1) Teaching of Auscultation. The Program Committee is gratified to announce that arrangements have been made for the repetition of the Special Cardiac Demonstration, using the electron cardio-scope, which was presented first in 1952 by Dr. J. Scott Butterworth, M.D., F.A.C.P., Associate Professor of Medicine, New York University Post-Graduate Medical School, New York, N. Y. The Cambridge Instrument Company, designers of the instrument, will provide the equipment and Dr. Butterworth is again managing the exhibit, being assisted by Maurice R. Chassin, M.D., F.A.C.P., Robert McGrath, M.D., F.A.C.P., Charles A. Poindexter, M.D., F.A.C.P., and Mr. C. E. Peterson, all of the New York University Post-Graduate Medical School.

An attempt is made with this exhibit to demonstrate the various auscultatory phenomena pertaining to the heart. These are recorded on tape and played through electronic stethophones to a large group. At the same time the simultaneous sound pattern, or stethogram, is visualized on the face of the Educational Electron Cardio-scope, which has a seventeen inch tube similar to a television set.

(2) Cardiac Silhouettes—This exhibit, also presented through the courtesy and coöperation of Dr. Butterworth, is presented in conjunction with the American Heart Association and uses models produced by the Heart Association. The exhibit is a combination of ten Fluorodemonstrators which are simple devices for allowing the individual to examine the silhouette of the heart in many positions as it would be seen in fluoroscopy and then to switch to "black light" illumination for direct visualization of the models.

Both exhibits, operating throughout the week, Arena Floor, Convention Hall, to the north of the Registration Bureau.

Post-Convention Forum Cruise to Bermuda—Three previous Post-Convention Cruises of the American College of Physicians to Bermuda all proved successful and popular. This cruise offers to members of the College and to their families and

friends an opportunity for discussions, rest, relaxation and amusement. A scientific forum for a portion of the time in the morning or the afternoon on shipboard is planned, making this cruise an integral part of the Annual Session. A special program will be published, but the tentative program includes scientific motion picture presentations on "Angiocardiography," "Use of Compound F in Rheumatic Disease," "A New Beginning," a film on rehabilitation from the Institute of Physical Medicine and Rehabilitation of the New York University—Bellevue Medical Center, "Kidney Function in Health" and "Kidney Function in Disease," from the Research Laboratories of Eli Lilly and Company, "Anemia," by William Dameshek, M.D., F.A.C.P., a Squibb medical film, and "Malnutrition in the Hospital Patient," by Eugene F. Du Bois, M.D., F.A.C.P., and Robert Elman, M.D., and Herbert Pollack, M.D., F.A.C.P., a Squibb film. It is also hoped to include on the program a film entitled "They Live Again," produced by Metro-Goldwyn-Mayer, which depicts the story of insulin, an especially appropriate film in view of the fact that Charles H. Best, M.D., of Toronto, will be the recipient of the 1953 John Phillips Memorial Award of the College. "New Frontiers of Medicine," a film prepared by the March of Time Forum, is also on the tentative program. A special feature on the return voyage will be a series of Kodachrome films and lecture on "Medical Military Problems in the Far East," by Dr. Richard A. Kern, Philadelphia, Secretary-General of the College.

The "Queen of Bermuda," luxurious cruise ship, will sail from New York at 3:00 P.M., Saturday, April 18; arrive in Hamilton Harbor, Bermuda, on Monday morning, April 20, and leave Bermuda at 3:00 P.M. on Wednesday, April 22, arriving in New York on Friday, April 24. Hotel Princess and Hotel Bermudiana will be official headquarters in Bermuda. This cruise provides perfect relaxation after a strenuous meeting, and Bermuda at this time of year is at its best. Special folders containing plan of ship, rates, etc., may be obtained from the Cruise Director, Mr. Leon V. Arnold, 36 Washington Square West, New York 11, N. Y. Make reservations early!

ENTERTAINMENT OF VISITING WOMEN

The Ladies' Entertainment Committee extends a cordial welcome to the wives and daughters of the members of the American College of Physicians. Headquarters for registration, information, tickets, reservations for entertainment, and all other women's activities, will be at Haddon Hall.

Daily Program

Sunday, April 12

2:00 P.M. to 4:30 P.M. Registration: Haddon Hall.

9:00 P.M. Concert by The Philadelphia Orchestra, Warner Theater. Admission by card; compliments of Schering Corporation.

Monday, April 13

9:00 A.M. to 4:30 P.M. Registration: Haddon Hall.

3:00 P.M. to 5:00 P.M. Welcoming Tea in honor of Mrs. T. Grier Miller, given by the Ladies' Committee, Rutland Room of Haddon Hall. Reservations necessary; complimentary.

9:00 P.M. An evening of divertissement with stars of radio, television, screen and stage. Ballroom, Convention Hall. Admission by ticket or badge; complimentary.

Tuesday, April 14

9:00 A.M. to 4:30 P.M. Registration: Haddon Hall.

9:30 A.M. Trip to Longwood Gardens. Bus leaves Haddon Hall for Wilmington, Del. Luncheon at duPont Country Club. Return to Haddon Hall by approximately 6:00 P.M. Tickets, \$6.00, including transportation, luncheon and admission to Gardens.

11:00 A.M. Tour of Haddon Hall kitchens. Tickets available at Registration Desk.

2:00 P.M. Aquatic Tour. See Atlantic City from the ocean by boat. One and one-half hour cruise. Bus transportation from Haddon Hall to dock and return. Tickets, \$1.75.

Wednesday, April 15

9:00 A.M. to 4:30 P.M. Registration: Haddon Hall.

10:15 A.M. "What's New at duPont's," 1121 Boardwalk (in front of Haddon Hall). Tickets available at Registration Desk.

12:30 P.M. Luncheon and Give-Away-Wardrobe Fashion Show, by The Needle-craft Shop-on-the-Boardwalk of Atlantic City, Carolina Room, Chalfonte Hotel. Tickets, \$4.50.

8:30 P.M. Annual Convocation of the College, Ballroom, Convention Hall.

10:15 P.M. President's Reception and Ball, Vernon Room, Haddon Hall.

Thursday, April 16

9:00 A.M. to 12:00 M. Registration: Haddon Hall.

10:00 A.M. Shopping Tour of South Jersey Antique Shops by private car. Reservations limited. \$3.00, including luncheon.

10:30 A.M. Aquatic Tour. See Atlantic City from the ocean by boat. One and one-half hour cruise. Bus transportation from Haddon Hall to dock and return. Tickets, \$1.75.

11:00 A.M. Tour of Haddon Hall kitchens. Tickets available at Registration Desk.

1:00 P.M. Lunch at Smithville Inn. One of the old landmarks in South Jersey. Transportation can be arranged if requested at time ticket is purchased at the Registration Desk. Reservations limited.

2:45 P.M. "What's New at duPont's," 1121 Boardwalk (in front of Haddon Hall). Tickets available at Registration Desk.

8:00 P.M. Annual Banquet of the College, Carolina Room, Chalfonte Hotel.

Color Televised Clinics—The program of color televised clinics has been materially extended at this meeting to take the place in some measure of the hospital clinic program which is not available, due to curtailed hospital facilities in Atlantic City. These televised clinics are furnished through the courtesy of Smith, Kline & French Laboratories, Philadelphia. The program is continuous, except for half hour intermissions, daily, Tuesday through Friday, April 14-17, and will be shown on the Arena Floor of Convention Hall.

"Meet the Expert"—As a new feature on the program, a series of lectures by recognized experts will be given concurrently with the Panel Discussions from 9:00 A.M. to 10:30 A.M., Tuesday and Thursday, April 14 and 16, and are designated on the chart showing the Panel Discussions and Clinical-Pathological Conferences with the prefix "ME" before the number.

The Technical Exhibit—The Technical Exhibit will be located in the main Arena of Convention Hall, and will be one of the best conducted by the College. The Committee on Exhibits maintains the highest possible standards in the conduct of this Exhibit. Exhibitors are admitted only by invitation. Irrelevant exhibits are eliminated, and only firms which present a group of approved products or services of scientific interest to the internist and allied specialist may exhibit.

Members and guests of the College are encouraged to accord the exhibitors courteous and interested attention. Many thousand dollars are expended by the exhibitors to bring to this College superior displays and up-to-date information concerning pharmaceuticals, equipment, medical books and medical services. The Technical Exhibitors gauge this meeting by the amount of interest shown and the co-operation displayed by the College.

Exhibits will be open from 8:45 A.M. to 5:30 P.M., daily, Monday through Thursday, and from 8:45 A.M. to 2:30 P.M., on Friday. Physicians are urged to use the intermission in the program for inspection of the exhibits, but these intermissions are inadequate for a thorough visit and inspection of the large number of exhibits, and thus physicians are encouraged to spend some additional time in this important part of the meeting.

PARTIAL LIST OF TECHNICAL EXHIBITORS

	<i>Booth</i>
Abbott Laboratories, North Chicago, Ill.	101-102
American Hospital Supply Corporation, Evanston, Ill.	133
American Journal of Medicine, New York, N. Y.	82
Ames Company, Inc., Elkhart, Ind.	43
Doris Appel Medical Sculptures, Lynn, Mass.	2
Appleton-Century-Crofts, Inc., New York, N. Y.	23
Armour Laboratories, The, Chicago, Ill.	106-107
Association of American University Presses, New York, N. Y.	18
Ayerst, McKenna & Harrison Limited, New York, N. Y.	117
W. A. Baum Co., Inc., Copiague (L. I.), N. Y.	104
Becton, Dickinson and Company, Rutherford, N. J.	36, 129
Bilhuber-Knoll Corp., Orange, N. J.	78
Ernst Bischoff Company, Inc., The, Ivoryton, Conn.	134
Blakiston Company, The, New York, N. Y.	12
Brewer & Company, Inc., Worcester, Mass.	9
Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N. Y.	108
Burton, Parsons & Co., Inc., Washington, D. C.	46
Cambridge Instrument Co., Inc., New York, N. Y.	5
S. H. Camp & Company, Jackson, Mich.	10
Chicago Dietetic Supply House, Inc., The, Chicago, Ill.	79
Chilean Iodine Educational Bureau, Inc., New York, N. Y.	112
Ciba Pharmaceutical Products, Inc., Summit, N. J.	71-72
Warren E. Collins, Inc., Boston, Mass.	52
County Surgical Co., Inc., Brooklyn, N. Y.	130
Davies, Rose & Company, Limited, Boston, Mass.	35
F. A. Davis Company, Philadelphia, Pa.	92

Booth

Desitin Chemical Company, Providence, R. I.	110
Devereux Schools, Devon, Pa.	81
DeVilbiss Company, The, Somerset, Pa.	83
Doak Company, Inc., Cleveland, Ohio	14
Doho Chemical Corporation, New York, N. Y.	41-42
Dome Chemicals, Inc., New York, N. Y.	90
Duke Laboratories, Inc., Stamford, Conn.	55
Edin Company, Inc., Worcester, Mass.	131
J. H. Emerson Company, Cambridge, Mass.	40
Fellows Medical Mfg. Co., Inc., New York, N. Y.	29
Fenwal Laboratories, Inc., Framingham, Mass.	13
C. B. Fleet Co., Inc., Lynchburg, Va.	76
Geigy Pharmaceuticals, New York, N. Y.	59-60
General Electric Co., X-Ray Department, Milwaukee, Wis.	19
General Foods Corp., New York, N. Y.	16, 33
Gerber Products Company, Fremont, Mich.	100
Grune & Stratton, Inc., New York, N. Y.	80
Hanova Chemical and Manufacturing Company, Newark, N. J.	111
Harrover Laboratory, Inc., The, Jersey City, N. J.	119
H. J. Heinz Company, Pittsburgh, Pa.	74
Paul B. Hoeber, Inc., New York, N. Y.	47
Hoffmann-La Roche, Inc., Nutley, N. J.	51
Hollister-Stier Laboratories, Inc., Spokane, Wash.; Los Angeles, Calif.; Chicago, Ill.; Philadelphia, Pa.	11
Hyland Laboratories, Los Angeles, Calif.	6
Irwin, Neisler & Company, Decatur, Ill.	34
Ives-Cameron Company, Inc., New York, N. Y.	58
Jones Metabolism Equipment Co., Chicago, Ill.	68
LaMotte Chemical Products Company, Baltimore, Md.	65
Lea & Febiger, Philadelphia, Pa.	105
Lederle Laboratories Division, American Cyanamid Company, New York, N. Y.	20-21-22
Eli Lilly and Company, Indianapolis, Ind.	97-98-99
J. B. Lippincott Company, Philadelphia, Pa.	132
Little, Brown & Company, Boston, Mass.	75
Macmillan Company, The, New York, N. Y.	45
Massachusetts Indemnity Insurance Company, Boston, Mass.	50
S. E. Massengill Company, The, Bristol, Tenn.	57
McNeil Laboratories, Inc., Philadelphia, Pa.	84
Mead Johnson & Company, Evansville, Ind.	91
Medco Products Company, Tulsa, Okla.	17
Medical Bureau, The, Chicago, Ill.	120

	<i>Booth</i>
Medical Case History Bureau, New York, N. Y.	126
Medical Film Guild, Ltd., New York, N. Y.	1
Merck & Co., Inc., Rahway, N. J.	85-86
Wm. S. Merrell Company, The, Cincinnati, Ohio	89
C. V. Mosby Co., New York, N. Y.; St. Louis, Mo.; San Francisco, Calif.	28
National Drug Company, The, Philadelphia, Pa.	109
Nepera Chemical Co., Inc., Yonkers, N. Y.	118
Oxford University Press, Inc., New York, N. Y.	128
Parke, Davis & Company, Detroit, Mich.	113-114-115-116
Chas. Pfizer & Co., Inc., Brooklyn, N. Y.	77
Riker Laboratories, Inc., Los Angeles, Calif.	15
A. H. Robins Company, Inc., Richmond, Va.	121
Rystan Company, Inc., Mount Vernon, N. Y.	88
Sanborn Company, Cambridge, Mass.	63-64
Sandoz Chemical Works, Inc., New York, N. Y.	103
Saranac Lake Medical Facilities, Inc., Saranac Lake, N. Y.	24
W. B. Saunders Company, Philadelphia, Pa.	123-124
Schenley Laboratories, Inc., Lawrenceburg, Ind.	25
Schering Corporation, Bloomfield, N. J.	44
G. D. Searle & Co., Chicago, Ill.	66
Sharp & Dohme, Inc., Philadelphia, Pa.	53-54
Smith, Kline & French Laboratories, Philadelphia, Pa.	38-39
E. R. Squibb & Sons, Division of Mathieson Chemical Corporation, Long Island City, N. Y.	67
Stetherton Sales Company, Wenonah, N. J.	135
Taylor Instrument Companies, Rochester, N. Y.	61-62
Travenol Laboratories, Inc., Morton Grove, Ill.	56
U. S. Vitamin Corporation, New York, N. Y.	136
Vanpelt & Brown, Inc., Richmond, Va.	8
Varick Pharmacal Company, Inc., New York, N. Y.	73
Walker Laboratories, Inc., Mount Vernon, N. Y.	37
Wallace & Tiernan Products, Inc., Belleville, N. J.	7
Warner-Chilcott Laboratories, New York, N. Y.	48-49
White Laboratories, Inc., Kenilworth, N. J.	3
Williams & Wilkins Company, The, Baltimore, Md.	4
Winthrop-Stearns Inc., New York, N. Y.	69-70
Woodward Medical Personnel Bureau, Chicago, Ill.	87
Wyeth Incorporated, Philadelphia, Pa.	125
Year Book Publishers, Inc., The, Chicago, Ill.	122

OUTLINE OF THE ATLANTIC CITY SESSION
 (All Events at Convention Hall, except President's Reception and Banquet)

April 13-17, 1953

TIME	MONDAY April 13	TUESDAY April 14	WEDNESDAY April 15	THURSDAY April 16	FRIDAY April 17
9:00 A.M. to 10:30 A.M.	Free Registration, Exhibits, etc.	"Meet the Expert" (4) Panels (5) Color Televised Clinics	Symposia (2) Color Televised Clinics	"Meet the Expert" (4) Panels (5) Color Televised Clinics	Symposia (2) Color Televised Clinics
10:30 A.M. to 11:00 A.M.		Intermission	Intermission	Intermission	Intermission
11:00 A.M. to 12:30 P.M.		Panels (5) C-P Conferences (2) Color Televised Clinics	Panels (5) C-P Conferences (2) Color Televised Clinics	Panels (5) C-P Conferences (2) Color Televised Clinics	Panels (5) C-P Conferences (2) Color Televised Clinics
2:00 P.M. to 5:00 P.M. (30-minute intermissions mid-afternoon)	1st General Session	2nd General Session	3rd General Session	Annual Business Meeting 4th General Session	5th General Session
Evening	Entertainment Stars of Radio, Screen, TV, and Stage			7:45 Pre-Convocation Assembly 8:30 Convocation 10:15 President's Reception and Ball	Banquet

9:00 P.M., Sunday, April 12, Philadelphia Orchestra Concert at Warner Theater.

GENERAL SESSIONS PROGRAM

Ballroom, Convention Hall

FIRST GENERAL SESSION**Monday Afternoon, April 13, 1953**

Presiding Officer

HILTON S. READ, F.A.C.P., Atlantic City, General Chairman

P.M.**2:00 Address of Welcome:**

The Honorable JOSEPH ALTMAN, Mayor of Atlantic City.

Response to Address of Welcome:

T. GRIER MILLER, F.A.C.P., President, The American College of Physicians.

Presiding Officer

President T. GRIER MILLER, F.A.C.P., Philadelphia

2:20 The James D. Bruce Memorial Lecture on Preventive Medicine: Influenza; The Newe Acquayantance.

THOMAS FRANCIS, JR., M.D. (by invitation), Chairman of Department of Epidemiology, University of Michigan Medical School.

2:55 The Current Studies of Malaria as a World Problem.

LOWELL T. COGGESHALL, F.A.C.P., Dean, Division of Biological Sciences, University of Chicago.

3:15 INTERMISSION.**3:45 The Diagnosis and Management of Epidemic Hemorrhagic Fever.**

THOMAS A. HAEDICKE (Associate), Chief, Medical Section, Veterans Administration, Atlanta.

Discussion by FRANCIS W. PRUITT, F.A.C.P., Colonel, (MC), USA; Chief of Medical Service, Letterman Army Hospital; San Francisco.

4:10 Fundamental Concepts in the Diagnosis of Sprue.

RAFAEL RODRIGUEZ-MOLINA, F.A.C.P., Assistant Professor of Tropical Medicine, School of Tropical Medicine, University of Puerto Rico; Chief, Medical Section, Veterans Administration Hospital; San Juan.

Discussion by DANIEL S. ELLIS (Associate), Assistant in Medicine, Harvard Medical School.

4:30 A Basic Classification of Porphyria: Certain Diagnostic and Therapeutic Considerations.

CECIL J. WATSON, F.A.C.P., Professor of Medicine, University of Minnesota Medical School.

4:50 ADJOURNMENT.

SECOND GENERAL SESSION

Ballroom, Convention Hall

Tuesday Afternoon, April 14, 1953

Presiding Officer

MAURICE C. PINCOFFS, M.A.C.P., Baltimore

P.M.**2:00 Periodic Health Examinations.**

FREDERICK H. SHILLITO, F.A.C.P., Instructor in Medicine, Columbia University College of Physicians and Surgeons; Medical Director, Pan-American Airways; New York.

2:20 Medical Significance of Illness and Absenteeism in Industrial Population.

NORMAN PLUMMER, F.A.C.P., Assistant Professor of Clinical Medicine, Cornell University Medical College; Medical Director, New York Telephone Company.

2:40 Acute Idiopathic Pericarditis.

EDWIN M. GOYETTE, F.A.C.P., Colonel, (MC), USA, Fitzsimons Army Hospital, Denver.

3:00 The Prevention and Control of Poliomyelitis.

JOSEPH STOKES, JR., M.D. (by invitation), Professor of Pediatrics, University of Pennsylvania School of Medicine.

3:20 INTERMISSION.**3:50 Anticoagulant Treatment of Myocardial Infarction (A Summary of the Final Report of the Committee on Anticoagulants of the American Heart Association).**

IRVING S. WRIGHT, F.A.C.P., Professor of Clinical Medicine, Cornell University Medical College.

4:10 Relationship of Adiposity to Serum Cholesterol and Lipoprotein and Their Modification by Dietary Means.

WELDON J. WALKER, F.A.C.P., Lieutenant Colonel, (MC), USA, Madigan Army Hospital, Fort Lewis, Wash.

4:30 The Current Status of 72 Patients with Severe Hypertension Subjected to Adrenal Resection and Sympathectomy.

WILLIAM A. JEFFERS, F.A.C.P., Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine.

4:50 ADJOURNMENT.

THIRD GENERAL SESSION

Ballroom, Convention Hall

Wednesday Afternoon, April 15, 1953

Presiding Officer

CHARLES F. MOFFATT, F.A.C.P., Montreal

P.M.**2:00 The John Phillips Memorial Lecture: The Action of Insulin.**

CHARLES H. BEST, M.D. (by invitation), Professor of Physiology and Director of Banting and Best Department of Research Medicine, University of Toronto School of Medicine.

2:40 Blood Sugar Metabolism in Adults in Georgia.

LESTER M. PETRIE, F.A.C.P., Lecturer in Industrial Hygiene, and CHRISTOPHER J. MCLOUGHLIN, F.A.C.P., Assistant in Medicine, Emory University School of Medicine, Atlanta.

Discussion by HUGH L. C. WILKERSON, F.A.C.P., Chief, Diabetes Section, Federal Security Agency, U. S. Public Health Service, Boston.

3:00 Idiopathic Hypoparathyroidism: General Considerations and Clinical Description of Concurrent Parathyroid and Adrenocortical Insufficiencies.

MARTIN M. HOFFMAN (Associate), Research Professor of Medicine, Dalhousie University Faculty of Medicine, Halifax.

3:20 INTERMISSION.**3:50 Advances in Antibiotic Therapy.**

JAMES W. HAVILAND, F.A.C.P., Clinical Assistant Professor of Medicine, University of Washington School of Medicine, Seattle.

4:10 Management of Upper Gastro-intestinal Hemorrhage.

THOMAS A. WARTHIN, F.A.C.P., Clinical Professor of Medicine, Tufts College Medical School; Associate Chief of Medical Service, Veterans Administration Hospital; Boston.

4:30 The Relationship of Chronic Ulcerative Colitis and Cirrhosis of the Liver.

FREDERICK W. HOFFBAUER (Associate), Associate Professor of Medicine, University of Minnesota Medical School.

Discussion by J. ARNOLD BARGEN, F.A.C.P., Professor of Medicine, University of Minnesota (Mayo Foundation).

4:50 ADJOURNMENT.

ANNUAL CONVOCATION

Wednesday Evening, April 15, 1953

8:30 O'Clock

Ballroom, Convention Hall

LEMUEL C. McGEE, Marshal

Pre-Convocation Assembly of Fellows to be inducted, Officers, Regents and Governors, at 7:45 P.M., Ballroom Floor, south corridor (rear of Ballroom Stage).

All members of the profession and the general public are cordially invited. No admission tickets required.

1. Processional.
2. The President's Address: "Responsibilities of the Fellows of The American College of Physicians." T. GRIER MILLER.
3. Conferring of Fellowships by the President.
4. Conferring of Masterships by the President.

5. Presentation of the John Phillips Memorial Medal for 1953.
6. Presentation of the James D. Bruce Memorial Medal for 1953.
7. Presentation of the Alfred Stengel Memorial Award for 1953.
8. Announcement of Research Fellows for 1953-54.
9. Announcement of Latin-American Fellows for 1952-53.
10. Announcement of A. Blaine Brower Traveling Scholars for 1953.
11. Convocation Oration: "Changing Trends in Internal Medicine." ROGER I. LEE, M.A.C.P., Boston.
12. Recessional.

The President's Reception and Ball will follow at 10:15 o'clock in the Vernon Room of the Haddon Hall Hotel. A cordial invitation is extended to all members and guests, with their families.

FOURTH GENERAL SESSION

Ballroom, Convention Hall

Thursday Afternoon, April 16, 1953

P.M.

2:00 ANNUAL BUSINESS MEETING.

All Fellows and Masters are urged to be present and to participate more actively in the administrative problems of the College. Reports will be received from the Secretary-General, Executive Secretary and Treasurer; elections of new Officers, Regents and Governors will take place; President-Elect LeRoy H. Sloan, of Chicago, Ill., will be inducted as President and will make a brief inaugural address.

2:40 INTERMISSION.

Presiding Officer

WALTER B. MARTIN, F.A.C.P., Norfolk, Va.

3:10 Detection and Treatment of the Effects of "Nerve Gas."

A. McGEEHEE HARVEY, F.A.C.P., Professor of Medicine, Johns Hopkins University School of Medicine.

3:30 Treatment of Common Cerebral Vascular Accidents.

JOHANNES M. NIELSEN, F.A.C.P., Clinical Professor of Neurology and Psychiatry, University of Southern California School of Medicine.

3:50 The Present Status of the Gout Problem.

ALEXANDER B. GUTMAN, F.A.C.P., Professor of Medicine, Columbia University College of Physicians and Surgeons.

4:10 Chronic Sodium Chloride Toxicity: Hypertension, Renal and Vascular Lesions.

GEORGE R. MENEELY, F.A.C.P., Assistant Professor of Medicine, Vanderbilt University School of Medicine.

Discussion by EUGENE A. STEAD, JR., F.A.C.P., Professor of Medicine, Duke University School of Medicine.

4:30 The Treatment of Hemochromatosis by Massive Venesection.

WILLIAM D. DAVIS, JR., F.A.C.P., Instructor in Clinical Medicine, and
WILLIAM R. ARROWSMITH, M.D., (by invitation), Assistant Professor of
Clinical Medicine, Tulane University of Louisiana School of Medicine.

4:50 ADJOURNMENT.

Thursday Evening, April 16, 1953

7:00 o'Clock

Lounge, Hotel Chalfonte

"DUTCH TREAT" COCKTAIL PARTY

8:00 o'Clock

Carolina Room, Hotel Chalfonte

THE ANNUAL BANQUET OF THE COLLEGE

Toastmaster:

HILTON S. READ, F.A.C.P., Atlantic City

Address of the Day:

"The Superstitions of the Pennsylvania Dutch"

LUTHER M. SCHAEFFER, Northampton, Pa.

FIFTH GENERAL SESSION

Ballroom, Convention Hall

Friday Afternoon, April 17, 1953

Presiding Officer

PAUL F. WHITAKER, F.A.C.P., Kinston, N. C.

P.M.

2:00 Recent Studies on ACTH and Cortisone.

GEORGE W. THORN, F.A.C.P., Professor of Medicine, Harvard Medical School.

2:20 Intra-articular Hydrocortisone in the Treatment of Arthritis.

JOSEPH L. HOLLANDER, F.A.C.P., Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine.

2:40 Clinical Differentiation of Functional and Organic Hypoglycemia.

ROBERT H. DURHAM, F.A.C.P., Physician-in-Charge, Division of General Medicine, Henry Ford Hospital, Detroit.

3:00 INTERMISSION.**3:30 An Evaluation of Bed Rest in the Treatment of Acute and Chronic Liver Disease.**

RICHARD B. CAPPS, F.A.C.P., Assistant Professor of Medicine, Northwestern University Medical School.

3:50 Malignant Lymphomas of the Gastro-intestinal Tract.

EDWIN L. LANE, F.A.C.P., Chief of Radiology, and R. PHILIP CUSTER, M.D.
(by invitation), Pathologist, Presbyterian Hospital, Philadelphia.

4:10 Smoker's Asthma: A Clinical Syndrome.

GEORGE L. WALDBOTT, F.A.C.P., Chief, Section of Allergy, Harper Hospital,
Detroit.

4:30 ADJOURNMENT.

MORNING SYMPOSIA

Wednesday, April 15, 1953

I. SYMPOSIUM ON EMOTIONAL FACTORS IN DISEASE

Ballroom, Convention Hall

Moderator

WILLIAM C. MENNINGER, F.A.C.P., Professor of
Psychiatry, Menninger Foundation School
of Psychiatry, Topeka

A.M.

9:00 Introduction by the Moderator.**9:10 Physiological Pathology Related to the Emotions.**

EDWARD WEISS, F.A.C.P., Professor of Clinical Medicine, Temple University
School of Medicine.

9:30 Social Factors in Illness.

JOHN MINOR, F.A.C.P., Associate in Medicine, George Washington University
School of Medicine.

9:50 Emotional Forces in Organic Disease.

KENNETH E. APPEL, F.A.C.P., Professor of Psychiatry, University of
Pennsylvania School of Medicine.

10:00 Psychotherapy by the Internist.

HENRY W. BROSN, F.A.C.P., Professor of Psychiatry, University of Pittsburgh
School of Medicine.

10:30 ADJOURNMENT.

II. SYMPOSIUM ON TUBERCULOSIS

Room C, Arena Floor, Convention Hall

Moderator

JAMES J. WARING, M.A.C.P., Professor Emeritus of Medicine,
University of Colorado School of Medicine

A.M.

9:00 Introduction by the Moderator.**9:10 Primary Serofibrinous Pleural Effusion in Army Personnel.**

WILLIAM H. ROPER, F.A.C.P., Hospital Medical Management Adviser,
Division of Tuberculosis Control, New York State Department of Health,
Albany, and JAMES J. WARING.

9:30 Late Results of Non-Resectional Treatment of Solitary, Dense, Tuberculous Pulmonary Foci.
ROGER S. MITCHELL, F.A.C.P., Associate Medical Director, Trudeau Sanatorium, Trudeau, N. Y.

9:50 Late Results in Resection of Localized Tuberculous Lesions of the Lung.
CARL W. TEMPEL, F.A.C.P., Colonel, (MC), USA, Chief of Medical Services, JAMES H. FORSEE, SR., F.A.C.P., Colonel, (MC), USA, Chairman of Research and Development Board, and EDWIN L. SCOTT (by invitation), Major, (MC), USA, Resident in Pathology; Fitzsimons Army Hospital, Denver.

10:10 Review of Chemotherapy in Tuberculosis.
J. BURNS AMBERSON, F.A.C.P., Professor of Medicine, Columbia University College of Physicians and Surgeons.

10:30 ADJOURNMENT.

Friday, April 17, 1953

III. SYMPOSIUM ON CARDIAC SURGERY

Ballroom, Convention Hall

Moderator

CHARLES C. WOLFERTH, F.A.C.P., Professor of Medicine,
University of Pennsylvania School of Medicine

A.M.

9:00 Introduction by the Moderator.

9:20 The Use of Angiocardiography in Candidates for Valvular Surgery.
HARRY F. ZINSSER, JR., M.D. (by invitation), Assistant Clinical Professor of Medicine, University of Pennsylvania School of Medicine.

9:40 Abnormal Cardiac Rhythms Associated with Cardiac Surgery and Their Treatment.
J. SCOTT BUTTERWORTH, F.A.C.P., Associate Professor of Medicine, New York University Post-Graduate Medical School.

10:00 Problems in Cardiac Surgery.
ALFRED BLALOCK, F.A.C.S. (by invitation), Professor of Surgery, Johns Hopkins University School of Medicine.

10:30 ADJOURNMENT.

IV. SYMPOSIUM ON ANEMIA

Room C, Arena Floor, Convention Hall

Moderator

CHARLES A. DOAN, F.A.C.P., Dean, Professor of Medicine and Director of Medical Research, Ohio State University College of Medicine.

A.M.

9:00 The Macrocytic Nutritional Anemias.
ROBERT W. HEINLE, M.D. (by invitation), Kalamazoo, Mich.

9:20 **Drug Induced Hypoplastic Anemia and Related Syndromes.**
EDWARD E. OSGOOD, F.A.C.P., Professor of Medicine, University of Oregon Medical School.

9:40 **Fecal Urobilinogen Excretion in Hemolytic Anemia.**
PAUL S. HAGEN (Associate), Assistant Professor of Medicine, University of Minnesota Medical School.

9:55 **Pseudo-Anemias.**
SLOAN J. WILSON, F.A.C.P., Associate Professor of Medicine, University of Kansas School of Medicine.

10:10 **The Use of Radioisotopes in Hematology.**
JOSEPH F. ROSS, F.A.C.P., Associate Professor of Medicine, Boston University School of Medicine.

10:30 ADJOURNMENT.

PANEL DISCUSSIONS, CLINICAL-PATHOLOGICAL CONFERENCES AND "MEET THE EXPERT" LECTURES

Topics of intimate interest and practical value to all members of the profession have been chosen after consulting scores of College members. Qualified men have been selected as moderators and members of the panel personnel. All panels are scheduled from Tuesday through Friday—from 9:00 A.M. to 12:30 P.M., Tuesday, April 14, and Thursday April 16; from 11:00 A.M. to 12:30 P.M., Wednesday, April 15, and Friday, April 17. Panels are indicated on the following charts with the prefix "P" before the number. Applicants may submit in writing three weeks before the Session, through the Executive Secretary of the College, any questions concerning any phase of the subjects listed under the Panel Discussions. Moderators and panel personnel will answer those questions which they feel are applicable to the subject under discussion and will answer as many questions as time permits.

Clinical-Pathological Conferences are scheduled concurrently with the Panel Discussions, from 11:00 A.M. to 12:30 P.M., Tuesday through Friday, April 14-17, and are designated on the following charts with the prefix "CP" before the number. The clinical protocols of interesting medical cases will be discussed by the participants who are expected to make the correct diagnosis. The postmortem findings will then be presented by the pathologist in whose department the case was autopsied. Moderators and conference personnel will then answer questions that may arise as time permits. The clinical protocols of the cases to be presented will appear in a separate booklet to be sent with the formal program, so that members may have the opportunity of making their own diagnoses before the formal conferences.

An innovation on the scientific program will be eight three-quarter hour "Meet the Expert" Lectures, for which have been selected authorities who can evaluate and editorialize the literature and research. These "Meet the Expert" Lectures are indicated on the following charts with the prefix "ME" before the number.

Applications for tickets to Panel Discussions and "Meet the Expert" Lectures, unless otherwise indicated in the final program, may be made in advance by members on a regular application form which will accompany the program. Tickets will also be available at the Registration Bureau, Convention Hall. Non-Members may not register by mail, but should secure their tickets directly at the meeting.

PANEL DISCUSSIONS, "MEET THE EXPERT," AND CLINICAL-PATHOLOGICAL CONFERENCES

Capacity	Ballroom, 2nd Floor Convention Hall (Admission by badge; no tickets)		Room A, Arena Floor Convention Hall (Admission by ticket only)		Room B, Arena Floor Convention Hall (Admission by badge; no tickets)		Room C, Arena Floor Convention Hall (Admission by badge; no tickets)		Room D, Arena Floor Convention Hall (Admission by badge; no tickets)		Room 20, 3rd Floor Convention Hall (Admission by ticket only)	
	5,000	450	1,000	600	1,000	1,000	1,000	500	500	450	450	450
Tuesday April 14	P-1 Emotional Factors in Gastro- intestinal Diseases Moderator *H. L. Bockus Philadelphia	P-2 Radiological Infor- mation, Please Moderator *W. E. Chamberlain Philadelphia	P-3 Poliomyelitis—Its Present Status Moderator John R. Paul New Haven	P-4 Recent Advances in Therapy Other Than ACTH Moderator George B. Kelle Philadelphia	P-5 Emotional Problems of Adolescence Moderator S. S. English Philadelphia	P-6 The Anticoagulants Lecturer *Janey Smith Detroit	P-7 Post-Gastricotomy Sequelae Lecturer T. E. Machella Philadelphia	ME-9 (9:45) Arthritis Lecturer R. H. Freyberg New York	ME-10 (9:45) Arthritis Lecturer George E. Burch New Orleans	ME-11 (9:45) Arthritis Lecturer R. H. Steele Philadelphia	ME-12 (9:45) Arthritis Lecturer R. H. Steele Philadelphia	ME-13 (9:45) Arthritis Lecturer R. H. Steele Philadelphia
9:30 A.M. to 10:30 A.M.	Thomas P. Almy New York Sarah M. Jordan Boston J. P. Quigley Memphis Howard P. Rome Rochester	W. McE. Pendergrass Philadelphia Paul Swenson Philadelphia	W. McE. Hammont Pittsburgh Howard A. Howe Baltimore P. M. Stinson New York Jos. Stokes, Jr. Philadelphia	W. McE. Caldwell M.C.U.S. Army Sherman Little Buffalo *J. W. Shadie, Jr. Butler, Pa. *H. F. Steele Philadelphia	Harry Beckman Milwaukee Harry Gold New York Mark Nickerson Ann Arbor	W. McE. Caldwell M.C.U.S. Army Sherman Little Buffalo *J. W. Shadie, Jr. Butler, Pa. *H. F. Steele Philadelphia	W. McE. Caldwell M.C.U.S. Army Sherman Little Buffalo *J. W. Shadie, Jr. Butler, Pa. *H. F. Steele Philadelphia	INTERMISSION	INTERMISSION	INTERMISSION	INTERMISSION	INTERMISSION
10:30 A.M. to 11:00 A.M.	INTERMISSION	CP-10 Clinical-Pathological Conference Moderator Howard P. Lewis	P-12 Recent Advances in the Medical Treat- ment of Tubercu- losis Moderator *W. G. Leaman Philadelphia Roy W. Scott Cleveland	P-13 The Present Status of Clinical Hematology Moderator *B. K. Wiseman Columbus *F. J. Bethell East Orange *F. L. Badger Boston J. M. Chamberlain Pathologist *H. R. Edwards New York W. S. Schwartz	P-14 Atherosclerosis and Hypercholesterolemia Moderator Louis N. Katz Chicago *David P. Barr New York Alice Keys Minneapolis Jeremiah Stamler Chicago	P-15 Common Fevers that Vex the Patient and the Doctor Moderator *R. C. Kimbrough, Jr. Knoxville *C. L. Brown Philadelphia *C. S. Kester Boston *R. P. McCombs Boston	P-16 The Internist and Ad- ministrative Problems of a General Hospital Moderator *J. C. Leonard Hartford D. G. Anderson *O. J. Buxaero Watertown C. C. Clay Orange *P. F. Larcheri Philadelphia *J. F. Pesel Trenton	INTERMISSION	INTERMISSION	INTERMISSION	INTERMISSION	INTERMISSION
Tuesday April 14	11:30 A.M. to 12:30 P.M.	CP-11 (11:45) Moderator John T. King Baltimore	INTERMISSION	INTERMISSION	INTERMISSION	INTERMISSION	INTERMISSION	INTERMISSION	INTERMISSION	INTERMISSION	INTERMISSION	INTERMISSION

* F.A.C.P. ** M.A.C.P.

PANEL DISCUSSIONS, "MEET THE EXPERT," AND CLINICAL-PATHOLOGICAL CONFERENCES

Capacity	Ballroom, 2nd Floor Convention Hall (Admission by badge; no tickets)	Room A, Arena Floor Convention Hall (Admission by ticket only)	Room B, Arena Floor Convention Hall (Admission by ticket only)	Room C, Arena Floor Convention Hall (Admission by badge; no tickets)	Room D, Arena Floor Convention Hall (Admission by badge; no tickets)	Room 20, 3rd Floor Convention Hall (Admission by ticket only)	Room 21, 3rd Floor Convention Hall (Admission by ticket only)	
Wednesday April 15 9:00 A.M. 10:30 A.M.	5,000	450	600	1,000	1,000	500	450	
10:30 A.M. 11:00 A.M.	Symposium on Emotional Factors in Disease			11 Symposium on Tuberculosis				
	INTERMISSION							
Wednesday April 15 11:00 A.M. 12:30 P.M.	CP 18 Clinical Pathological Conference	P 30 Protein and Perme- ability Factors in the Genesis of Edema	P 21 Rehabilitation	P 22 The Management of The Individual Who Has Had a Cere- bral Occlusion	P 23 Emotional Factors in Disease	P 24 Endocrinology	P 25 Endocrinology	
	Moderator *W. F. Strong Vanderbilt R. A. Minella St. Louis C. S. Sturgis Ann Arbor	Moderator *S. H. Armstrong Chicago J. A. Schoenberger Chicago	Moderator H. A. Rank New York J. G. Benzon New York Irving Cooper New York D. A. Court New York G. G. Dwyer New York M. Newson New York E. A. Layman New York Morton Marks New York	Moderator *H. A. Rank New York J. G. Benzon New York Irving Cooper New York D. A. Court New York G. G. Dwyer New York M. Newson New York E. A. Layman New York Morton Marks New York	Moderator *R. H. Lyons Syracuse L. F. Bishop, Jr. New York J. W. Pitt Pittsburgh J. J. Sanborn San Francisco H. J. Stewart New York	Moderator *Edward Weiss Philadelphia D. W. Mitchell New York George Ham Chapel Hill W. C. Menninger Topeka Stewart Wolf Oklahoma City	Moderator *R. F. E. Camilli San Francisco F. S. Gordon Madison T. H. McGavack New York F. W. H. Perloff Philadelphia Edward Rose Philadelphia	Moderator *R. T. Beebe Albuquerque R. F. E. Camilli San Francisco F. S. Gordon Madison T. H. McGavack New York F. W. H. Perloff Philadelphia Edward Rose Philadelphia

* F.A.C.P., ** M.A.C.P., § Associate.

PANEL DISCUSSIONS, "MEET THE EXPERT," AND CLINICAL-PATHOLOGICAL CONFERENCES

Ballroom, 2nd Floor Convention Hall 'Admission by badge; no tickets)	Room A, Arena Floor Convention Hall 'Admission by ticket only)	Room B, Arena Floor Convention Hall 'Admission by badge;	Room C, Arena Floor Convention Hall 'Admission by badge;	Room D, Arena Floor Convention Hall 'Admission by badge;
Capacity 5,000	450	P-27 Allergy	P-28 Electrolytes	P-29 Chronic Fatigue
Moderator Mr. R. Harrison Birmingham Carl Binger New York W. V. Elbert Minneapolis Mr. P. Johnson M.C., S. Army R.L. McMillan Winston-Salem J. Reeves Beaumont Stamford	Moderator Mr. M. Davison Atlanta H. A. Abramson New York J. H. Mitchell Columbus J. M. Sheldon Ann Arbor Oscar Sweetford Charlotteville	Moderator Mr. W. Houston Houston J. R. Elkinton Philadelphia Carol Handley Houston E. January Iowa City K. G. Kohlbaas Indianaapolis A. J. Merrill Atlanta G. Thorpe Kay New Orleans	Moderator Mr. W. Houston Houston J. R. Elkinton Philadelphia W. H. Desner McLean U. S. Army S. Portis Beverly Hills H. C. Shands Boston	Moderator Mr. M. Durant Philadelphia N. Allan Boston C. M. MacLeod New York C. A. Ragan New York H. Ramkempamp Cleveland
Thursday April 16 9:00 A.M. to 10:30 A.M.	P-36 Differential Diagnosis of Chest Pain	P-37 Fibrosis and Non-Arthritic Rheumatism	P-38 Headache	P-39 Antibiotics
Capacity 5,000	450	INTERMISSION	INTERMISSION	INTERMISSION
10:30 A.M. to 11:00 A.M. Thursday April 16	CP-35 Clinical Pathological Conference	P-40 Liver Disease	INTERMISSION	INTERMISSION
11:00 A.M. to 12:30 P.M.	Moderator W. R. Adams Chicago E. A. Stead, Jr. Durham E. V. Sydenstricker Augusta	Moderator Mr. W. Boland Los Angeles J. J. Bunim Bethesda Wallace Graham Toronto W. D. Robinson Ann Arbor Otto Steinbrocker New York Edward Weiss Philadelphia	Moderator C. S. Keeler Boston J. W. Haviland Seattle Mary H. Loveless New York J. M. McLean New York Bronson Ray New York	Moderator Mr. W. Cayer Winston-Salem R. B. Capps Chicago H. P. Lewis Portland J. D. Hughes Memphis M. J. Ronanaky Washington
Capacity 5,000	450	INTERMISSION	INTERMISSION	INTERMISSION
Friday April 17 9:00 A.M. to 10:30 A.M.	CP-46 Pathologist	P-41 Thrombophlebitis	INTERMISSION	INTERMISSION
Capacity 5,000	450	J. F. A. McManus Birmingham	J. F. A. McManus Birmingham	J. F. A. McManus Birmingham
Friday April 17 11:00 A.M. to 12:30 P.M.	J. F. A. McManus Birmingham J. F. A. McManus Birmingham	O. H. P. Pepper Philadelphia M. A. Bhansali Cincinnati W. B. Poor Richmond	J. H. Comroe, Jr. Philadelphia Lewis Dexter Boston	Meyer Neide Philadelphia G. H. Pratt New York Armand Quick Milwaukee
Capacity 5,000	450	INTERMISSION	INTERMISSION	INTERMISSION
Saturday April 18 9:00 A.M. to 10:30 A.M.	CP-47 Pathologist	P-42 Thrombophlebitis	INTERMISSION	INTERMISSION
Capacity 5,000	450	J. F. A. McManus Birmingham J. F. A. McManus Birmingham	J. H. Comroe, Jr. Philadelphia Lewis Dexter Boston	J. H. Comroe, Jr. Philadelphia Lewis Dexter Boston
Saturday April 18 11:00 A.M. to 12:30 P.M.	J. F. A. McManus Birmingham J. F. A. McManus Birmingham	P-43 Recent Advances in Cardiopulmonary Physiology	INTERMISSION	INTERMISSION
Capacity 5,000	450	J. H. Comroe, Jr. Philadelphia Lewis Dexter Boston	J. H. Comroe, Jr. Philadelphia Lewis Dexter Boston	J. H. Comroe, Jr. Philadelphia Lewis Dexter Boston
Saturday April 18 1:00 P.M. to 2:30 P.M.	J. F. A. McManus Birmingham J. F. A. McManus Birmingham	P-44 Selection of Patients for Cardiac Surgery	INTERMISSION	INTERMISSION
Capacity 5,000	450	J. H. Comroe, Jr. Philadelphia Lewis Dexter Boston	J. H. Comroe, Jr. Philadelphia Lewis Dexter Boston	J. H. Comroe, Jr. Philadelphia Lewis Dexter Boston

* F.A.C.P., M.A.C.P., Associate.

PANEL DISCUSSIONS, "MEET THE EXPERT," AND CLINICAL-PATHOLOGICAL CONFERENCES

	Ballroom, 2nd Floor Convention Hall (Admission by badge; no tickets)	Room A, Arena Floor Convention Hall (Admission by ticket only)	Room C, Arena Floor Convention Hall (Admission by badge; no tickets)	Room 20, 3rd Floor Convention Hall (Admission by ticket only)
Capacity	5,000	450	600	1,000
Friday April 17 9:00 A.M. to 10:30 A.M.	III Symposium on Cardiac Surgery		IV Symposium on Anemia	
10:30 A.M. to 11:00 A.M.	INTERMISSION	INTERMISSION	INTERMISSION	INTERMISSION
	CP-43 Clinical-Pathological Conference	P-45 The Present Status of the Management of Diabetes Mellitus	P-46 The Internist and Citizenship Responsibilities	P-47 Bleeding Lesions of the Gastro-Intestinal Tract
Friday April 17 11:30 A.M. to 12:30 P.M.	Moderator *W. M. Johnson J. M. Kinsman Louisville *O. O. Meyer Madison	Moderator *Priscilla White Boston *G. G. Duncan Philadelphia L. E. Hinkle New York F. D. W. Lukens Philadelphia *I. A. Mirsky Pittsburgh *R. M. Wilder Bethesda	Moderator *L. H. Bauer Hempstead *George Baehr New York *J. T. Boone Washington E. L. Crosby Chicago R. V. Lee Palo Alto H. S. Vance South Bend	Moderator *J. A. Bangen Rochester *A. H. Aaron Buffalo *J. L. Borland Jacksonville *E. N. Collins Cleveland *G. G. McHardy New Orleans *T. A. Warthin West Roxbury
	CP-44 (11:45)	Moderator *J. A. Greene Houston *E. L. Borts Philadelphia *L. A. Greig Pittsburgh Pathologist *P. A. Herbut Philadelphia		

* F.A.C.P.

† Associate.

Moderator
*G. H. Gehrmann
Wilmington
S. D. Bacon
New Haven
*C. N. Davis
Philadelphia
J. S. Heavlin
T. F. Hoagland
Wilmington
*F. Redwick Lemere
Seattle

Color Television of Medical Clinics

The following series of clinics will be televised in color daily, Tuesday through Friday mornings, between 9:00 A.M. and 12:30 P.M., to eighteen receiving booths in Convention Hall by a group of physicians and institutions from various parts of the country. In some instances complete portions of the television program have been allotted to specific institutions, such as the Brooke Army Medical Center, the Bronx Veterans Administration Hospital, the University of Oklahoma School of Medicine, the Bowman Gray School of Medicine, and others.

Due to changing programs from one clinic to another, a slight lag will occur. However, it is believed that the times indicated will be approximately correct.

Admission by regular badge; no special tickets required.

Tuesday, April 14, 1953

9:00- 9:25 **Therapeutic Interview.**
MARC J. MUSSER, F.A.C.P., Associate Professor of Medicine, University of Wisconsin Medical School.

9:25- 9:45 **Neurological Medicine.**
BERNARD J. ALPERS, F.A.C.P., Professor of Neurology, Jefferson Medical College of Philadelphia.

9:45-10:00 **TEM.**
FRANKLIN R. MILLER (Associate), Associate Professor of Medicine, Jefferson Medical College of Philadelphia; Assistant Director of Division of Hematology, Jefferson Medical College Hospital; and JOHN S. FLINT, M.D. (by invitation), Fellow in Hematology, Jefferson Medical College Hospital.

10:00-10:10 **The Gammagram.**
HERBERT C. ALLEN, JR., M.D. (by invitation), Assistant Professor of Medicine, Baylor University College of Medicine; Director, Radioisotope Unit, Veterans Administration Hospital, Houston.

10:10-10:30 **The Artificial Kidney.**
PAUL E. TESCHAN (by invitation), Captain, (MC), USA, MARION E. McDOWELL (Associate), Major, (MC), USA, and FRANK L. BAUER (Associate), Lieutenant Colonel, (MC), USA, Medical Division of the Army Medical Service Graduate School and Medical Service, Walter Reed Army Hospital, Army Medical Center, Washington.

10:30-11:00 **INTERMISSION.**

11:00-11:15 **Visiting Chief Pro Tem Rounds at the Atlantic City Hospital.**
ALEXANDER MARBLE, F.A.C.P., Clinical Associate in Medicine, Harvard Medical School, and Physician, New England Deaconess Hospital.

11:15-11:30 **Treatment of Rheumatoid Arthritis.**
L. MAXWELL LOCKIE, SR., F.A.C.P., Professor of Therapeutics and Head of the Department, University of Buffalo School of Medicine.

11:30-12:00 **The Cardiac in Employment.**
LAURITZ S. YLVISAKER, F.A.C.P., Vice President and Medical Director, Fidelity Mutual Life Insurance Company, Philadelphia.

12:00-12:15 **Psychiatric Aspects of the Male Menopause.**
GEORGE N. RAINES, F.A.C.P., Captain, (MC), USN, Head, Neuropsychiatry Branch, Professional Division, Bureau of Medicine and Surgery, Navy Department; Professor of Psychiatry and Director of the Department, Georgetown University School of Medicine.

12:15-12:30 **Late Results in the Treatment of Ulcerative Colitis with Corticotropin.**

C. WILMER WIRTS, F.A.C.P., Assistant Professor of Medicine, Jefferson Medical College of Philadelphia, and Chief, Gastro-intestinal Clinic, Jefferson Medical College Hospital.

Wednesday, April 15, 1953

9:00- 9:45 **The Brooke Army Medical Center Presents:**

1. **Rectal Biopsy in Diagnosis of Schistosomiasis.**

BENJAMIN H. SULLIVAN, JR. (Associate), Lieutenant Colonel, (MC), USA.

2. **Combat Psychiatry.**

A. J. GLASS (by invitation), Colonel, (MC), USA.

3. **Nocturnal Paroxysmal Hemoglobinuria.**

ROBERT E. BLOUNT, F.A.C.P., Colonel, (MC), USA.

4. **The Solitary Pulmonary Nodule.**

J. R. VIVAS (by invitation), Lieutenant Colonel, (MC), USA.

5. **Scalene Node Biopsy in Diagnosis of Diseases of the Chest.**

CLINTON A. PIPER (by invitation), Captain, (MC), USA.

9:45-10:00 **Rehabilitation of Peripheral Nerve Injuries.**

FRANK E. NULSEN, M.D. (by invitation), Assistant Professor of Neurosurgery, University of Pennsylvania School of Medicine.

10:00-10:30 **Rehabilitation.**

HOWARD A. RUSK, F.A.C.P., and Staff, Professor of Rehabilitation and Physical Medicine and Chairman of the Department, New York University College of Medicine.

10:30-11:00 **INTERMISSION.**

11:00-11:15 **Visiting Chief Pro Tem Rounds at the Atlantic City Hospital.**

CHARLES A. DOAN, F.A.C.P., Professor of Medicine, Ohio State University College of Medicine.

11:15-11:30 **Fractional Epidural Block—Its Use in the Control of Pancreatic Pain and Demonstration of Technique.**

J. EDWARD BERK, F.A.C.P., Assistant Professor of Medicine, and LEROY W. KRUMPERMAN, M.D. (by invitation), Professor of Anesthesiology, Temple University School of Medicine.

11:30-11:45 **Rehabilitation of the Tuberculous.**

ROBERT CHARR, F.A.C.P., Assistant Professor of Medicine, Jefferson Medical College of Philadelphia, and Director of X-Ray Surveys, Philadelphia Tuberculosis and Health Association.

11:45-12:00 **The Physical Examination.**

LOUIS KRAUSE, F.A.C.P., Professor of Clinical Medicine, University of Maryland School of Medicine.

12:00-12:15 **A Practical Clinical Method for the Study of Acid-base Balance.**

ANDREW YEOMANS, F.A.C.P., Assistant Professor of Clinical Medicine, Dartmouth Medical School, and Chief of Medical Service, Veterans Administration Center; and GEORGE H. STUECK, JR., M.D. (by invitation), Assistant Chief of Medical Service and Chief of Research, Veterans Administration Center, White River Junction, Vt.

12:15-12:30 **Critical Appraisal of the Anticonvulsants.**

LAWRENCE I. KAPLAN, M.D. (by invitation), Instructor in Neurology, New York University College of Medicine, and Attending Neurologist and Director of Neurological Service, Hospital for Joint Diseases.

Thursday, April 16, 1953

9:00- 9:45 **The Bronx Veterans Administration Hospital Presents:**1. **Proctology for the Internist.**

SYDNEY JAMPEL (Associate), Chief, Proctology and Gastroenterology.

2. **Use of Primaquine in Radical Cure of Vivax Malaria.**

JOSEPH GENNIS (Associate), Assistant Chief of Medical Service.

3. **The Hemagglutination Test for Rheumatoid Arthritis.**

ABRAHAM S. JACOBSON (Associate), Chief of Medical Section A.

4. **Trauma in Relation to Coronary Thrombosis.**

LOUIS A. KAPP, F.A.C.P., Chief of Cardiac Section, Medical Service.

9:45-10:30 **The University of Oklahoma School of Medicine Presents:**1. **Talking with the Patient.**

STEWART WOLF, M.D. (by invitation), Professor and Head of the Department of Medicine.

2. **Sternal Marrow Aspiration.**

ROBERT M. BIRD, M.D. (by invitation), Associate Professor of Medicine.

3. **Relation of Flicker Frequency to Arterial Oxygen Saturation.**

ROBERT A. SCHNEIDER, M.D. (by invitation), Assistant Professor of Medicine and Psychiatry.

10:30-11:00 **INTERMISSION.**11:00-11:15 **Visiting Chief Pro Tem Rounds at the Atlantic City Hospital.**

HAROLD J. JEGHERS, F.A.C.P., Professor of Medicine and Director of the Department, Georgetown University School of Medicine; Physician-in-Chief, Georgetown University Hospital.

11:15-11:30 **Physical Medicine and Rheumatology.**

WALTER M. SOLOMON, F.A.C.P., Senior Clinical Instructor in Medicine, Western Reserve University School of Medicine; President, American Congress of Physical Medicine and Rehabilitation.

11:30-11:45 **Isotopes.**

JOSEPH F. ROSS, F.A.C.P., Associate Professor of Medicine, Boston University School of Medicine, and GERALD HINE, Ph.D. (by invitation), Research Associate, Department of Physics, Massachusetts Institute of Technology.

11:45-12:00 **Unilateral Renal Ischemia ("Goldblatt Kidney") with Nephrectomy and Three-Year Cure of Malignant Hypertension.**

JOSEPH T. ROBERTS, F.A.C.P., Chief, Cardiology Section, Veterans Administration Hospital, and Lecturer in Medicine, University of Buffalo School of Medicine.

12:00-12:15 **The Present Methods for Treating Bronchiectasis.**
ROGER O. EGEBERG (Associate), Clinical Professor of Medicine, University of California Medical School at Los Angeles, and Chief of Medical Service, Wadsworth Veterans Administration Hospital.

12:15-12:30 **Grief and Abnormal Grief Response.**
ERICH LINDEMANN, M.D. (by invitation), Massachusetts General Hospital, Boston.

Friday, April 17, 1953

9:00- 9:15 **Amebiasis.**
HENRY E. HAMILTON (Associate), Assistant Professor of Internal Medicine, State University of Iowa College of Medicine.

9:15- 9:30 **Anterior Pituitary Insufficiency.**
H. ST. GEORGE TUCKER, JR., F.A.C.P., Assistant Professor of Medicine, Medical College of Virginia.

9:30- 9:45 **Progressive Systemic Sclerosis (Scleroderma).**
THEODORE B. BAYLES, F.A.C.P., Clinical Associate in Medicine, Harvard Medical School; Director of Research, Robert Breck Brigham Hospital.

9:45-10:30 **The Bowman Gray School of Medicine of Wake Forest College Presents:**

1. **Myxedema—Diagnosis and Treatment.**
GEORGE T. HARRELL, JR., F.A.C.P., Research Professor of Medicine.
2. **Management of Gout.**
HENRY L. VALK (Associate), Instructor in Medicine, and ERNEST H. YOUNT (Associate), Associate Professor of Medicine.
3. **Diagnostic and Research Aspects of Liver Biopsy.**
DAVID CAYER, F.A.C.P., Associate Professor of Medicine.

10:30-11:00 **INTERMISSION.**

11:00-11:15 **Visiting Chief Pro Tem Rounds at the Atlantic City Hospital.**
THOMAS M. DURANT, F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine.

11:15-11:30 **Strokes.**
WALTER O. KLINGMAN, F.A.C.P., Associate Professor of Neurology and Psychiatry, University of Virginia Department of Medicine.

11:30-11:45 **The Deep Mycoses.**
ARTHUR C. CURTIS, F.A.C.P., Professor of Dermatology and Syphilology and Director of the Department, University of Michigan Medical School.

11:45-12:00 **Vertigo.**
GEORGE A. WOLF, JR., F.A.C.P., Dean and Professor of Clinical Medicine, University of Vermont College of Medicine.

12:00-12:15 **Management of Occlusive Vascular Disease.**
A. WILBUR DURVEE, F.A.C.P., Professor of Clinical Medicine, New York University Post-Graduate Medical School, Attending Physician and Chief of Peripheral Vascular Clinic, University Hospital, and Attending Physician, Bellevue Hospital.

12:15-12:30 **Gastric Mucosal Disease with Special Reference to Gastroscopy and Gastroscopic Biopsy.**
SYDNEY SELESNICK, F.A.C.P., Gastro-enterologist, Veterans Administration Hospital, Newington, Conn.

THE ATLANTIC CITY STORY

Site of the 34th Annual Session of the American College of Physicians April 13-17, 1953

ATLANTIC CITY is signalized honored to be this year's annual meeting place for the American College of Physicians. Although the most successful and frequent A.M.A. meetings have been held here, and the Association of American Physicians and scores of other special medical groups enthusiastically return to our shores year after year, the dearth of clinical facilities and material in this fishing village of 65,000 souls had hardened the hearts of the College fathers against our wistful pleas. However, after the first colored Tele-Clinic broadcast from our Auditorium, successfully repeated throughout the Country, proved their practicability, the College conceded that "This is the place."

When Hendrik Hudson skirted our coast on his way to discover a river, he felt that our inland waterways about Absecon Island (on which Atlantic City now stands) were unsafe, and indeed, the local Lenni-Lenape Indians called them Absegami—"little waters," from which term Longfellow later corrupted "big sea waters" to Gitchi gumi. It remained for Dr. Jonathan Pitney to recognize the virtues of the island as a watering place, and in January, 1853, he persuaded the Camden & Atlantic Railroad Company to stretch its line from the mainland to the resort. The railroad president was John Chalmers DaCosta, whose son became the renowned Philadelphia surgeon. The Camden & Atlantic Land Company found that their engineer, Mr. Osborne, had lettered this area "Atlantic City" on their map, and this title was at once approved. The next year formalized its founding. A stone tablet in Columbus Plaza, Atlantic City, reads: "Atlantic City was founded as a health resort 1854 through the efforts of Dr. Pitney, physician, scholar, man of vision."

There are many reasons why Dr. Pitney's village health resort blossomed forth and has become the most popular vacation ground in the world. Its internationally famous beach offers an eight mile stretch of fine white sand, two to three hundred yards wide, of gradual slope far into the ocean, obviating the need for roped-off areas. Washed by an easy surf, with summer temperatures in the seventies, guarded by a celebrated beach patrol corps of one hundred star swimmers, safe from the dangers of game fish present in southern latitudes, hundreds of thousands of bathers daily during the season attest to the popularity of this best of all beaches—which is also the best resort attraction.

On June 26, 1870, Atlantic City dedicated the world's first Boardwalk, which is now five miles long. The first American picture postcard was introduced here in 1872. Its first City Hall was built in 1875. The volunteer fire department was organized in 1881, followed in 1882 by the water

works that pumped "spring water" across the meadows. The first electric car on Atlantic Avenue was authorized in 1889. The first modern hotel with baths and electric lights, the Windsor, was opened in 1890. The first rolling chair appeared here in 1896. The first boulevard across the meadows from the mainland came in 1905, and Atlantic Avenue was paved in 1907. Then in 1921 came the birth of the Miss America Pageant, with seven inter-city beauties, and the crowning of the first of a long succession of "Queens."

With the advent of the roaring Twenties came a fabulous gaiety, splendor and spending the like of which will probably never again be seen. Gambling



FIG. 1. Convention Hall, aerial view.

and high life brought notoriety and the dubious honor of being the "World's Playground." Since then, Atlantic City has matured, and has regained the dignity and distinction of being a great health, recreation and pleasure resort.

On May 31, 1929, Atlantic City dedicated the world's largest Auditorium, to provide recreation, entertainment, and a meeting place for conventions. Covering seven acres, and with almost unlimited facilities, the "Big Hall" has presented horse shows, football games, beauty pageants, dog racing, ice hockey and "Ice Capades," as well as many major conventions. Its ballroom and dozens of meeting rooms offer auxiliary sidelights to supplement the main events going on under the vast dome. By far the largest

and most powerful organ ever built is housed here. It is equipped with two giant consoles, one with seven manuals and the other, a moveable one with five. There are 1,255 speaking stops and 33,000 pipes ranging from three-sixteenths of an inch to 64 feet in length. It is run by a 365 H.P. group of motors, has seven blowers and its own generator. The wiring used would girdle the earth twice. Four years' time was necessary to complete this organ at a cost of \$500,000. The soundings are disposed in eight locations, all discernible from the main floor by reason of grille-screens which form the face of each chamber.



FIG. 2. Aerial view of Chalfonte-Haddon Hall, College Headquarters for this session.

The present organist can play six of seven manuals at one time, a feat never before accomplished by an organist. In addition to the huge main auditorium organ, there is a smaller one in the ballroom, which cost \$100,000.

In June, 1942, until early in 1945, the Auditorium was the headquarters for an Army Air Force Basic Training Center that eventually saw more than 400,000 men pass through its portals in their transition from civilian into Army life. Later it became headquarters for Redistribution Station No. 1 in the AAF, and remained "in the service" until 1945. Along with the Big Hall, the Army also occupied some 46 hotels and other units for housing and

supplies. Atlantic City, drafted into service, met the challenge by turning over its full facilities for the duration of World War II.

Many visitors to Atlantic City are more impressed by its magnificent hotels than by any other one thing and because of them return here each year, and numerous organizations meet here almost annually. This resort offers about 27,000 hotel rooms and an estimated 12,000 rooms in rooming houses or tourist cottages. Seventeen of the most palatial of the hotels, with over 5,000 de luxe rooms, are on the beachfront and tower high about the boardwalk in a setting which gives them an elegance seldom found elsewhere. They combine to give Atlantic City a skyline which probably takes second



FIG. 3. Aerial view of Chelsea Hotel, American Heart Association Headquarters.

place only to Manhattan Island in the tourist's book. The College headquarters will be at the Chalfonte-Haddon Hall, whose 1,000 sleeping rooms help make it the largest resort hotel property in the world. The tallest resort hotel, on the other hand, is the Claridge, which points its tower eighteen stories in the air. The Chelsea, headquarters for the American Heart Association meeting, has recently been modernized.

Each of the hotels is of a design and type of construction all its own. One may feature huge domes, like a castle in the Arabian Nights, another a tall Minaret, while a third gives prominence to a court of colorful flower beds. All have numerous large sundecks that look out over the boardwalk,



FIG. 4. Bird's-eye view of Atlantic City Beachfront looking East from Haddon Hall.

beach and far to sea. Resort hotel construction has not been pointed toward accommodating the greatest number of guests, but instead toward providing the ultimate in comfort, rest and relaxation for the patrons. This is emphasized in the rambling lobbies and lounges, the sun decks, and dining and game rooms. Good food is a "must" in the resort, for guests have more time to eat and enjoy their meals.

But while innkeeping is of necessity a major industry in Atlantic County, other industries flourish here as well. Even in Colonial days, huge sailing



FIG. 5. A section of Atlantic City Beachfront looking West from the Auditorium.

ships were built in Atlantic shipyards, bog iron was mined, forges turned out cannonballs for Washington's army and water pipes for Philadelphia; there were numerous saw mills, charcoal plants, grist mills, textile mills, and paper mills. The Atlantic Area Development Council in recent years has again encouraged business plants to locate here, where they will find 140 successful manufacturers as neighbors and more than 100 service industries, turning out a variety of products from armatures, barrels, baskets, batteries and beach umbrellas to tricycles, upholstering fabrics, vinyl film products, wearing apparel, and wooden toys.



FIG. 6. Atlantic City Hospital.

Medical Facilities

Although the Medical Society for the Colony of New Jersey, founded July 23, 1766, by seventeen physicians in New Brunswick to improve "the low state of affairs into which the practice of medicine has fallen" was the first of its kind in existence, it was not until June 7, 1880, that the Atlantic County Medical Society was founded by eight physicians: Drs. Job B.

Somers, D. B. Ingersoll, Willard Wright, E. H. Madden, E. B. Waters, T. H. Boysen, Boardman Reed and G. E. Abbott. Dr. Somers of Linwood was elected the first president; Dr. Boysen, Egg Harbor City, secretary and Dr. Madden, Absecon, Treasurer. The society now has about 135 members. Its president this year is Dr. R. D. Harley.

There are two general hospitals in the County, Atlantic City Hospital and Shore Memorial Hospital. In addition, specialized facilities are represented by the Clyde M. Fish Memorial Hospital, Children's Seashore Home, and the Betty Bacharach Home.

The Atlantic City Hospital was the first local facility established to care for the urgent medical needs of the growing community in the middle of the nineteenth century. It grew and moved several times before locating at its present site at 30 S. Ohio Avenue. Here new wings were gradually added



FIG. 7. Shore Memorial Hospital.

until it reached its present bed capacity of 242, of which 90 are public beds, plus 45 bassinets. All services are represented save contagion, psychiatric cases, neurosurgery and intricate chest surgery. In 1950, 9,200 patients were admitted; there were 1,650 deliveries, 4,500 surgical operations, representing 95,000 patient days. There were 43,000 visits to the dispensaries. There are 17 internes and residents, and the resident-interne training program, modernized seven years ago by Dr. Hilton Read, F.A.C.P., to include teaching by a new visiting chief each week, has gained national fame. The hospital is now bursting its seams and a new 300-bed modern hospital is projected for the near future.

The Shore Memorial Hospital, located in Somers Point, is a general hospital with general facilities, save for contagion, tuberculosis, or psychiatric problems. In its 70 beds and 10 bassinets, it cared for 2,250 patients this past year.

The Clyde M. Fish Memorial Hospital, formerly the Pine Rest Sanatorium, is equipped to treat all types of tuberculous diseases, sending its major surgery to the Atlantic City Hospital. Its 69 beds are always occupied, and its large staff is represented by many chiefs of service from the Atlantic City Hospital.

The Children's Seashore Home is a convalescent hospital for children, admitted through the Social Service Departments of Atlantic City, North



FIG. 8. Children's Seashore Home, now nearing completion.

Jersey, Philadelphia and suburbs of Philadelphia. There are special facilities, including a physiotherapy department, occupational therapy department, two school teachers, two visiting dentists, a complete laboratory, and an x-ray department. There is an overwhelming number of applications for its 70 beds, and the new building, soon to be completed, will house 108 patients.

The Betty Bacharach Home for Afflicted Children, located in Longport at the western tip of Absecon Island, specializes in the care of children with



FIG. 9. Betty Bacharach Home.

crippling diseases, such as poliomyelitis, rheumatic heart disease, spinal tuberculosis, etc. In 1951, 99 afflicted children were admitted for a total of 17,649 hospital days. While most of these were indigent cases, the average per diem rate per patient was \$7.33, with an average stay of 178 days. Costs were kept low because all physicians served without fee. Proposed additions to the Betty Bacharach Home will greatly increase its facilities.

There are numerous small nursing homes scattered in and around the County.

The General Chairman and his committees have left no stone unturned to make this 34th Annual Session of the American College of Physicians a memorable one. The scientific program, herewith published, speaks for itself. For entertainment the Committee has procured the Philadelphia Orchestra for one evening and has arranged other special entertainment events both for the men and for the women. However, individual members will find many other sources of diversion including chair rides and strolls on the boardwalk, selected night clubs, four very fine golf courses, horseback riding, theaters, etc.

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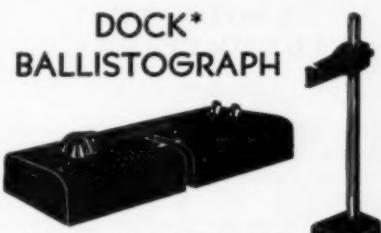
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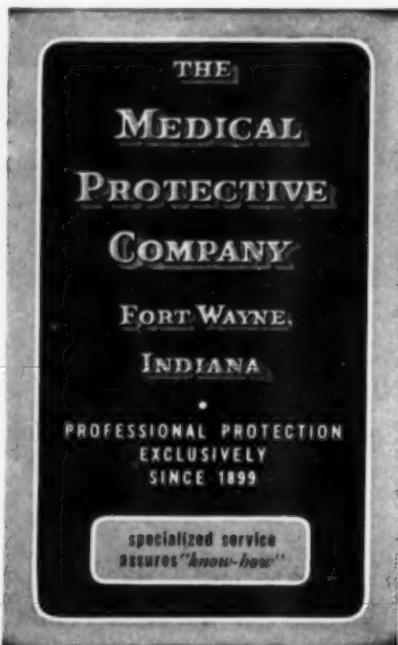
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Bibliography: 1. Barach, A.L., et al.: Bull. New York Acad. Med. 28:353 (June) 1952.

2. Flippin, H.F., et al.: Report distributed at the Chicago Session of the A.M.A. (June) 1952.

3. Segal, M.S., et al.: GP, in press.

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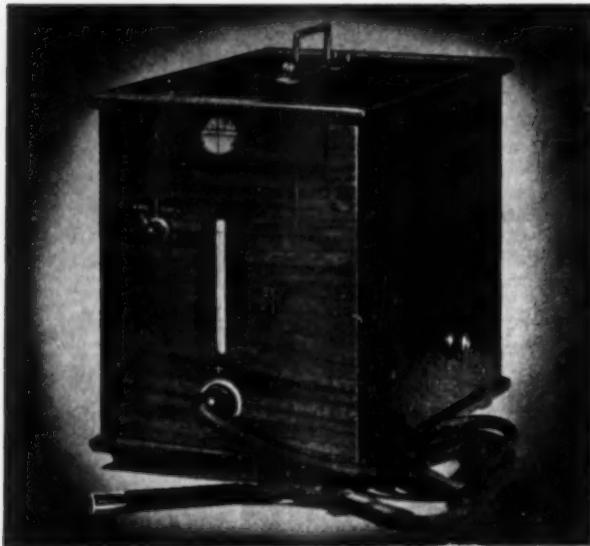
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